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SOME OBSERVATIONS ON HYPERSENSITIVENESS TO PNEUMOCOCCUS PROTEIN, WITH SPECIAL REFERENCE TO ITS RELATION TO IMMUNITY.

By Paul W. Clough, M. D.,

Associate in Medicine, The Johns Hopkins University, and Resident Physician, The Johns Hopkins Hospital.

(From the Biological Division of the Medical Clinic of The Johns Hopkins University.)

The experiments here reported were undertaken in order to determine, if possible, whether or not any constant relation exists between immunity to pneumococcus infection and hypersensitiveness to pneumococcus protein. The relationship of hypersensitiveness to immunity is not yet thoroughly understood. While at first glance the one is apparently the antithesis of the other, there is considerable evidence to show that they are often associated with one another, and that they may represent different manifestations of what is essentially a single process.

The extensive studies of the last 6 years on the reaction of the living body to injections of foreign protein have led to entirely new conceptions concerning immunity from infectious disease. While many of these conceptions were deduced by von Pirquet,[1] as a result of his clinical studies on serum disease and vaccinia, a sound experimental basis for them was first laid by the pioneer researches of Vaughan.[2] The essential features of Vaughan's theory have been embodied and further elaborated in the interesting theory independently advanced by Friedberger,[3] after a very extensive series of researches. According to this view, bacterial protein, like all foreign protein, is broken up in the circulation into simpler substances by means of specific ferments (Vaughan), or antibodies (amboceptor and complement, Friedberger). In the normal individual these ferments are present in minute amounts, and the rate of decomposition is slow. But as the result of the continued presence of a foreign protein in the circulation, there ensues a specific increase in the amount of the corresponding ferment, or antibody, in the blood. As a result, the foreign protein is broken up much more rapidly than in the normal individual. This increased rapidity of decomposition of the foreign protein may result in immunity, or hypersensitiveness, according to the circumstances in a given case.

The decomposition of the protein is a gradual process, a series of intermediate products being successively formed and broken down into still simpler ones. The native protein itself

is not directly toxic to the body, and the final end products are also quite harmless; but some of the intermediate decomposition products, related probably to peptone, are very poisonous. In the normal animal, the rate of decomposition is so slow that there are not enough of these poisonous intermediate products present at a given time to cause symptoms. In the allergic animal (infected, immunized, or sensitized) the increased rate of decomposition may give rise to the rapid formation of an intoxicating or even of a fatal dose of these poisons, if a large amount of the foreign protein suddenly enters the circulation. The breaking up of the foreign protein is to be regarded as a useful and necessary process; the intoxication as an unfortunate, accidental phenomenon which mars its course. If the foreign protein is one which is incapable of increasing after its introduction into the body, *e. g.*, horse serum, the accelerated decomposition offers no obvious advantage to the individual animal if the dose of the protein is small, whereas it may prove fatal to the animal if the dose is large. The animal is hypersensitive.

On the contrary, if the foreign protein is capable of increase after its entrance into the body, *i. e.*, if it is a living virus, the accelerated reaction usually will be beneficial, since it tends to make possible the rapid and complete destruction of the invading organisms, and thus prevents them from multiplying and giving rise to a fatal infection. The animal is therefore protected, or immune. But this protection depends entirely upon the fact that the quantity of living virus which gains access to the body at a given time, under natural conditions, is usually so small that it cannot yield a dangerous dose of the poison, however rapidly broken up. If the amount of living virus entering the body is large, if for example, it be comparable in amount to the quantity of serum required to intoxicate a sensitized animal, the "immune" animal will be acutely intoxicated, and will succumb much more quickly than a normal animal. The essential nature of the process is identical in the two cases, though it may be disastrous to the individual in one instance, but beneficial in another.

The general symptoms of infectious disease (aside from the action of the true soluble toxines) are attributed by Friedberger to these same poisons, formed as the result of the decomposition of the bacterial protein by specific antibodies (amboceptor and complement). In the normal animal there are no symptoms immediately following infection. The breaking up of the protein by the small amount of normal amboceptor present is too slow to liberate an appreciable dose of toxin. Symptoms appear only after specific antibodies have been formed in sufficient quantity to break up the bacterial protein rapidly. The appearance of symptoms would, therefore, imply the development of a certain degree of immunity.

This view Friedberger has supported by many ingenious experiments. The strongest proof he has advanced is the production *in vitro*, from bacteria, specific immune serum and complement (guinea-pig), of a poison which in large doses causes symptoms in normal guinea-pigs identical with those seen in a fatal anaphylactic reaction. In smaller doses it causes fever or subnormal temperature, according to the dose. Since the poison causes the same symptoms, from whatever species of organism or foreign protein it is derived, he regards it as a non-specific substance contained in every protein molecule, and has named it anaphylatoxin. The mechanism of its liberation is the only specific feature of the process. This view of the non-specificity of the toxin constitutes the only essential difference between his conception and Pfeiffer's older theory of endotoxines. According to this view of Friedberger, then, the symptoms of infectious disease may be regarded as due to a kind of chronic anaphylactic intoxication.

That a direct relationship or association exists between hypersensitiveness to bacterial protein and immunity to infection is most clearly shown in the case of organisms like B. typhosus and B. coli. This was indicated by the early work of Rosenau and Anderson,[4] and definitely demonstrated by Vaughan,[5] and others. Vaughan showed that guinea-pigs which had been sensitized by injections of bacterial extracts (colon and typhoid) were definitely more resistant to infection than normal animals.

That a hypersensitiveness to typhoid protein probably develops in man during the course of the disease, along with an immunity, is indicated by the occurrence of ophthalmic and cutaneous reactions (Chantemesse,[6] Austrian[7]).

This theory agrees very well with the facts, when applied to a disease like typhoid. It seems, *a priori*, probable that it would apply to a disease in which the immunity, in large part at least, depends on direct lysis of the bacilli by the serum. But its application is not so obvious in the case of a disease like pneumonia, in which the incubation period is probably very short; and where death in uncomplicated cases is due to a septicæmia, and may occur so early that any noteworthy antibody formation is impossible. Recent studies by Rosenow[8] show that if suspensions of pneumococci in serum or salt solution are incubated at 37° C. for a suitable length of time, toxic substances appear, probably as a result of autolysis, which cause symptoms in normal guinea-pigs identical with those caused by Friedberger's anaphylatoxin. The latter, moreover, may be formed by the application to the organisms of fresh normal guinea-pig serum alone, without immune serum. Friedberger attributes this to the presence of normal amboceptors in the serum. It is, therefore, unlikely that the appearance of symptoms in pneumococcus infections depends on the production of immune bodies.

Nevertheless, it is not improbable that such substances may play a rôle in recovery from the disease. The phenomena at crisis suggest a sudden "deintoxication" of the body. This is certainly not due to true antitoxin formation. It must involve the destruction of the invading micro-organisms, and might adequately be explained, simply by a resulting cessation in toxin formation. The evidence, too, is strongly in favor of the view that this destruction is the result of phagocytosis and intracellular digestion of the organisms. There is no appreciable degree of direct bactericidal or bacteriolytic power to be made out either in normal or pneumonic serum. However, it seemed possible that there might be an increased formation of those ferments, or antibodies, which break up the

pneumococcus protein and its toxic by-products, and that (as suggested by Rosenow[9]) this accelerated destruction of the poison might play a rôle in a deintoxication of the body at the crisis. If so, this might be associated with a demonstrable condition of allergy on the part of patient, and it might be capable of demonstration in properly immunized animals.

With this in view, several series of guinea-pigs were sensitized to extracts of pneumococci, or to killed cultures; while other series were immunized to living cultures. Both the immunity and hypersensitiveness were tested in each series. A pneumococcus protein was also prepared and applied to a series of patients, just as tuberculin is employed in the intracutaneous and ophthalmic tuberculin tests.

The pneumococcus strain used in these tests was isolated from the lung of a fatal case of pneumonia, and was kept at a high stage of virulence by frequent passages through animals. To obtain organisms in large quantity for sensitization work, the strain was cultivated in large flasks of 5 per cent glucose broth, to which finely powdered (not precipitated) calcium carbonate was added. The flasks were shaken occasionally during incubation. After 24 to 36 hours, when the maximum growth was reached, the flasks were shaken up, allowed to stand until the calcium carbonate had settled to the bottom, and the fluid was poured into tubes and centrifugalized. Smears were examined to demonstrate the purity of the culture. The supernatant fluid was decanted completely from the sedimented organisms, and the latter suspended in 50 cc. of sterile salt solution and again centrifugalized. The organisms were thus washed free from peptone and other disturbing constituents of the broth. The washing fluid was decanted completely and the sediment suspended in a few drops of distilled water and dried *in vacuo* over calcium chloride. Unless the desiccation was rapid, the end product was often unfit for use.

The dried residue was weighed and ground for 3 hours in an agate mortar, with a weighed amount of sterile sand, or salt. It was then extracted in salt solution (or in water, if ground in salt) 10 cc. of fluid being used for each gram of dried material. The best results (with this particular strain) were obtained by extracting at 37° C. for 18 hours. The extract was then centrifugalized for several hours at high speed, the fluid being decanted from time to time into a clean tube, till no further sediment was obtained. In some experiments the extract was used at once for sensitization or intoxication of the animals. In others the protein was precipitated from the extract by pouring the latter into 10 volumes of absolute alcohol; the precipitate was collected, dried *in vacuo*, and weighed. The material so obtained is a fine white powder, consisting largely of more or less altered protein. One gram of dried culture residue yields about 0.15 gm. of "protein."

During the process of extraction a considerable degree of autolysis takes place, as already pointed out by Rosenow. As a result the extracts become toxic, and on intravenous injection into normal guinea-pigs cause symptoms identical with those seen in an anaphylactic reaction. Prepared in this way, extracts become somewhat toxic after 18 hours' incubation, and still more markedly so after 24 to 36 hours. The toxicity is much reduced by heating for 1 hour at 60°, but it is not always entirely destroyed.

TABLE I.—TOXICITY OF EXTRACT FOR NORMAL GUINEA-PIGS ON INTRAVENOUS INJECTION.

No. of animal.	Wt. in gms.	Wt. in gms. of dried culture residue per 250 gms. of guinea-pig.	Time of extraction.	Heated.	Result.
14	250	0.020	18 hrs. 37° C.	Not heated.	0
15	255	0.030	" "	" "	0
5	390	0.040	" "	" "	+ 5 min.
4	275	0.040	" "	1 hr. 55–60° C.	0
6	390	0.040	" "	" "	0
189	340	0.060	" "	" "	+ 3 min.
7	335	0.060	" "	" "	0
9	250	0.060	" "	" "	0
8	325	0.068	" "	" "	0
22	270	0.080	" "	" "	0

Occasional irregularities, such as shown by No. 189, were not rarely encountered. These animals died after showing symptoms characteristic of anaphylactic shock, and showed at autopsy a maximal degree of acute distention of the lungs, as well as numerous subserous hæmorrhages, especially in the pericardium.

Sensitization was carried out by subcutaneous injections of suspensions of killed cultures, or of extracts of such suspensions. The best results were obtained from three injections of 0.02 gm. of dried residue at two-day intervals. Smaller amounts sensitized, but not constantly. An interval of at least 8 weeks was allowed to elapse after the last injection before intoxication was attempted. Sensitization lasted at least from 6 to 8 months.

In all the tests here reported, the injections of extracts made to test primary toxicity, or to intoxicate sensitized animals, were given directly into the jugular vein. The animals were anæsthetized, the vein was dissected out and ligatures were applied. Two to six hours later, after complete recovery, the animal was securely held and the injection made into the vein with a Record syringe, equipped with a fine hypodermic needle. It is quite unnecessary to tie in a canula, but a ligature is often necessary to prevent subsequent bleeding.

Animals which suffered an acute fatal reaction usually showed no symptoms until one or two minutes had elapsed after the injection. They then became restless, and showed rapidly increasing evidences of respiratory distress. After a transient period of accelerated breathing, the respiratory movements became slow, labored, and ineffectual, and it could easily be seen that very little air was entering the lungs. There was deep cyanosis, and often micturition and defecation occurred. Frequently, also, these movements were interrupted by sneezing, or by hiccoughs, which were often associated with spasmodic jumping, or bucking movements. After from three to six minutes, in fatal cases, the animals developed violent general clonic convulsions, which alternated with periods of deep coma. During these periods of coma, there were seen feeble, gasping, respiratory efforts, which became

more and more infrequent and finally ceased at least one to two minutes before the heart stopped beating.

At autopsy the lungs were extremely voluminous, and did not collapse at all when the chest was opened. They were light pink in color, and usually very dry on cross-section. Animals which died after longer intervals and normal animals, which succumbed to the direct toxic action of the extracts, tended to show a less acute degree of emphysema of the lungs, and more congestion and œdema than in the case of animals dying in acute anaphylactic shock. Often the pleural surfaces were mottled with dark purple areas of hæmorrhage. In nearly all cases hæmorrhages were found under the visceral pericardium, varying in size from a pin-point to 5-6 mm. in diameter.

In reactions which were not fatal, the characteristic symptoms were restlessness and respiratory disturbances, followed by weakness and a profound drop in temperature. But as normal control animals also often showed a drop in temperature after doses of extract but little larger than those required to intoxicate a sensitized animal, this symptom was not regarded as a trustworthy criterion of anaphylaxis, in this particular work.

The symptoms described differ somewhat from those characteristic of an anaphylactic reaction to horse serum. In particular one misses the evidences of cutaneous hyperæsthesia. There is only rarely much scratching or biting of the skin, or rubbing of the nose, so often seen in animals reacting to an injection of serum.

The intoxicating power of such extracts of pneumococci for previously sensitized animals is shown in the following table.

TABLE II.—SENSITIZATION WAS COMPLETED NOVEMBER 7, 1912. REINJECTIONS, JANUARY 15 AND 16, 1913.

No. of animal.	Wt. in gms.	Previous treatment.	Wt. in gms. of culture ex. tract per 250 gms. of guinea-pig.	Time of Extraction.	Heated	Result.	
						Reaction.	Outcome.
6	390	None.	0.040	18 hrs. 37° C.	1 hr. 55-60° C.	0	Lived.
7	335	"	0.060	" "	" "	0	Died in 24 hrs.
8	325	"	0.068	" "	" "	0	Lived.
158	470	Sensitized.	0.030	" "	" "	0	"
157	450	" "	0.030	" "	" "	+	Lived ½ hr.
41	250	" "	0.040	" "	" "	+ +	Lived.
154	460	" "	0.040	" "	" "	+ +	+ 5 min.
159	480	" "	0.040	" "	" "	+ +	" "
160	330	" "	0.060	" "	" "	+ +	" "

With suitable extracts it was possible to intoxicate sensitized guinea-pigs with doses that were materially less than those required to produce symptoms in normal control animals. The average dose required to intoxicate a sensitized animal was the extract from 0.040 gm. of dried culture residue for each 250 gms. of body weight. However, the margin between the fatal dose for a sensitized animal and that borne by a normal animal was never very large. There was some variation in the activity of different extracts, and marked variation in the reaction of different individual guinea-pigs to the same extract. It was, therefore, necessary to include several control animals and several treated animals in every test. The relatively large dose of extract required to intoxicate, and the large amount of time and labor required to secure even a small quantity of the extract restricted to an unexpected degree the scope of the experiments.

The various specimens of "protein" obtained by precipitation of such extracts showed still greater variation, both in their primary toxicity, and in their power of exciting true anaphylactic shock. It was necessary to test the antigenic property of each specimen by showing that it would intoxicate sensitized pigs in doses tolerated by normal animals, before using it on man.

The following table shows the properties of a suitable preparation of "protein" after it has been heated one hour at 60° C.

TABLE III.—REINJECTIONS MADE MARCH 29, 1912.

No. of animal.	Wt. in gms.	When sensitized.	Protein injected.	Result.		
				Reaction.	Outcome.	Autopsy.
80	415	Control.	0.040	0	+ 5 hrs.	Negative.
82	422	"	0.020	0	+ 5 hrs.	"
48	400	Dec. 22, 1911.	0.040	+ + +	+ 3-4 min.	Typical acute distention of the lungs.
24	400	" "	0.020	+ + +	+ 3-5 min.	Typical.
49	400	" "	0.020	+ + +	+ 3-5 min.	"
47	400	" "	0.010	+ + +	+ 3-5 min	"

Doses smaller than 0.010 gm. gave inconstant results and usually were not acutely fatal. Some preparations of protein, had to be discarded since the dose required fatally to intoxicate a sensitized animal was also fatal to a normal animal.

The precipitated protein possessed sensitizing as well as intoxicating power. A guinea-pig (No. 45) was sensitized Dec. 21, 1911, by a subcutaneous injection of 0.030 gm. of protein. On March 28, 0.020 gm. was reinjected intravenously, and caused a definite anaphylactic reaction, which, however, was not fatal. Two control pigs, receiving intravenous injections of 0.020 and 0.040 gm., respectively, of the same protein, showed no anaphylactic symptoms. Several other guinea-pigs, which had been given injections of 0.03 to 0.04 gm. of protein subcutaneously in order to sensitize them, emaciated and died after 3 or 4 weeks, apparently being poisoned by the injections.

In order to determine whether or not this condition of hypersensitiveness is specific, several series of guinea-pigs were sensitized as above described, (1) to a mixture of several strains of pneumococci, (2) to a single strain of pneumococcus, (3) to a mixture of several strains of *Str. pyogenes*, and (4) to a mixture of several strains of *Str. viridans*. Because of the spontaneous death of some of these guinea-pigs, during the incubation period in which hypersensitiveness was developing, and because some of the extracts did not give constant results, it was not possible to carry out a complete series of crossed sensitization and intoxication tests. Certain conclusions, however, can be drawn from an analysis of the results of this series.

An analysis of Table IV shows that it was possible to sensitize and to intoxicate guinea-pigs with the extract of a mixture of strains of several pneumococci, and with the ex-

TABLE IV.—THIS TABLE ILLUSTRATES THE ACTION OF EXTRACTS OF THE PNEUMOCOCCUS AND REPRESENTS A FEW RESULTS SELECTED FROM A LARGER SERIES.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected. (a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration.	(d) Heated.	Result. Reaction.	Outcome.	Autopsy.
25	360	Normal control.	Pneumococcus mixtures.	0.040	18 hrs. in ice box.	1 hr. 55° C.	0	Lived.	.....
121	460	Pneumococci; mixtures of strains.	" " "	0.040	" "	" "	+ + +	+ 7 min.	Typical lesions.
9	250	Normal control.	Pneumococcus (Gatches).	0.060	18 hrs. 37° C.	" "	0	Lived.	.....
154	460	Pneumococcus (Gatches).	" " "	0.040	" "	" "	+ + +	+ 5 min.	Typical.
124	450	Pneumococcus mixtures.	" " "	0.040	" "	" "	+	Lived.	.....

TABLE V.—THE ACTION OF EXTRACTS OF STR. PYOGENES.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected. (a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration.	(d) Heated.	Result. Reaction.	Outcome.	Autopsy.
79	270	Normal control.	Staph. pyogenes.	0.040	18 hrs. 37° C.	1 hr. 55° C.	0	Lived.	.....
112	500	" "	" "	0.060	" "	" "	0	"	.....
133	550	Str. pyogenes.	" "	0.040	" "	" "	0	"	.....
140	620	" "	" "	0.040	" "	" "	0	"	.....
141	670	" "	" "	0.060	" "	" "	+	+ over night.	Negative.
57	430	Str. viridans.	" "	0.060	" "	" "	0	Lived.	.....
93	270	Pneumococcus.	" "	0.060	" "	" "	0	"	.....

TABLE VI.—THE ACTION OF EXTRACTS OF STR. VIRIDANS.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected to intoxicate. (a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration of extraction.	(d) How heated.	Result. Reaction.	Outcome.	Autopsy.
113	300	Normal control.	Str. viridans.	0.060	18 hrs. 37° C.	1 hr. 55° C.	0	Lived.	.....
115	300	" "	" "	0.060	24 hrs. 37° C.	1 hr. 60° C.	0	"	.....
58	370	Str. viridans.	" "	0.060	18 hrs. 37° C.	1 hr. 55° C.	+ + +	+ 5 min.	Typical.
62	350	" "	" "	0.060	" "	" "	+ + +	" "	"
67	290	" "	" "	0.060	24 hrs. 37° C.	1 hr. 60° C.	+ +	.....	.....
95	300	Pneumococcus.	" "	0.060	18 hrs. 37° C.	1 hr. 55° C.	0	Lived.	.....
101	270	" "	" "	0.060	" "	" "	0	"	.....
142	660	Str. pyogenes.	" "	0.060	" "	" "	0	"	.....

TABLE VII.—THE ACTION OF EXTRACTS OF PNEUMOCOCCUS.

No. of animal.	Wt. in gm.	Species to which sensitized.	Extract injected to intoxicate. (a) Species.	(b) Wt. in gms. per 250 gms. of guinea-pig.	(c) Duration of extraction.	(d) How heated.	Result. Reaction.	Outcome.	Autopsy.
110	300	Normal control.	Pneumococcus (Gatches).	0.060	18 hrs. 37° C.	1 hr. 60° C.	0	Lived.	.....
78	250	" "	" " "	0.060	" "	" "	0	"	.....
77	260	" "	" " "	0.080	" "	" "	0	"	.....
53	330	Pneumococcus (Gatches).	" " "	0.060	" "	" "	+ + +	+ 5 min.	Typical.
180	530	" " "	" " "	0.060	" "	" "	+ +	Lived.	.....
94	340	Pneumococcus (Neufeld Pni).	" " "	0.060	" "	" "	+	"	.....
130	600	Str. pyog.	" " "	0.060	" "	" "	0	"	.....
59	500	Str. viridans.	" " "	9.060	" "	" "	0	"	.....
114	320	Normal control.	Pneumococcus (Sam).	0.060	" "	" "	0	.....	.....
74	300	" "	" " "	0.060	" "	" "	0	+ 2 hrs.	Negative.
22	710	Pneumococcus (Sam).	" " "	0.045	" "	" "	+ + +	+ 3 min.	Typical.
105	720	" " "	" " "	0.045	" "	" "	+ + +	+ 6 min.	"
100	280	Pneumococcus (Neufeld Pni).	" " "	0.060	" "	" "	0	Lived.	.....
64	410	Str. viridans.	" " "	0.060	" "	" "	±*	"	.....
66	440	" "	" " "	0.060	" "	" "	+ +	+ 5 min.	Typical.

* Showed slight symptoms.

tract of a single strain of pneumococcus. It was found also that a guinea-pig, which had been sensitized to a mixture of several strains of pneumococci, could be intoxicated with the extract of a single strain, not included in that mixture.

It was not possible acutely to intoxicate guinea-pigs with extracts of *Str. pyogenes* prepared in this manner. Occasionally mild anaphylactic symptoms were elicited. Thus, No. 141 (Table V) showed restlessness after the injection, defecation and micturition, occasional hiccoughs, and pronounced respiratory distress. After 50 minutes these symptoms subsided; the animal showed great weakness, and died during the night. The controls, as well as an animal sensitized to *Str. viridans*, and to a pneumococcus, showed no symptoms. There was only a feeble intoxicating power demonstrable and this seemed to be specific.

Table VI demonstrates that sensitized animals can be acutely and fatally intoxicated by injections of extracts of *Str. viridans*. The results also indicate a considerable degree of specificity in the reaction, since animals which had been sensitized to the pneumococcus and to *Str. pyogenes*, did not show any anaphylactic symptoms. However, pigs Nos. 95 and 101 probably were not maximally sensitized since some of the other members of this series did not react on injection of pneumococcus extract. (See Nos. 100 and 94 in Table VII.)

This table (VII) shows, again, that guinea-pigs which have been sensitized to pneumococcus, can be intoxicated acutely by an intravenous injection of an extract of pneumococci. Such an extract did not cause any anaphylactic symptoms on injection into a pig sensitized to *Str. pyogenes*, but did fatally intoxicate one out of three pigs sensitized to *Str. viridans*, and caused very mild anaphylactic symptoms in one of the other two. The reaction is, therefore, not absolutely specific, but quantitatively a certain degree of specificity is shown by a comparison of this series with that summarized in Table VI, since pigs sensitized to *Str. viridans* uniformly reacted to injections of the corresponding viridans extract.

These results apparently showed a rather higher degree of specificity in the reaction in the differentiation of the pneumococcus and streptococcus, than was described by Rosenow[9] and by Davis.[10] But the method of preparing the material for the intoxicating injection used in these experiments was so different from their methods that the results are scarcely comparable.

The following experiments were carried out in order to demonstrate, if possible, whether any relationship exists between hypersensitiveness to extracts of the pneumococcus and immunity to living pneumococci in guinea-pigs. For this work the virulent strain of pneumococcus, already described, was employed. It was carried through a long series of guinea-pigs to maintain a high degree of virulence and, if possible, to increase its virulence for this species.

One series of guinea-pigs was sensitized, as described, by three subcutaneous injections of 0.020 gm. of dried, killed cultures, given on alternate days. After several weeks, some of these were reinjected intravenously with extracts of pneumococci, as illustrated in Table II, and were shown to be highly sensitized. Other animals of the series (series B, Table VIII) were given subcutaneous injections of graduated doses of living virulent cultures to determine their degree of immunity. Rosenow[8] has shown that guinea-pigs suitably sensitized have a definite immunity of moderate degree to virulent pneumococci. This is to be expected, since it has long been known that a large dose of killed, virulent organisms produces a considerable degree of immunity in the rabbit.

Another series of pigs was immunized by repeated subcutaneous injections of small, increasing doses of living cultures. In some cases a single preliminary injection of killed organisms was given, followed later by injections of living organisms. One such dose of killed organisms alone did not cause the development of demonstrable hypersensitiveness. After a high degree of immunity had been secured, some animals of the series were given intravenous injections of an extract of pneumococci to determine whether hypersensitiveness also had developed. Other animals of this series (Series C, Table VIII) were given subcutaneous injections of living, virulent cultures to demonstrate that immunity had been produced.

The degree of immunity developed is illustrated by the following series:

TABLE VIII.

No. of animal.	Series A. Normal guinea-pigs.		Series B. "Sensitized" guinea-pigs.		Series C. "Immunized" guinea-pigs.	
	Dose in cc.	Result.	Dose in cc.	Result.	Dose in cc.	Result.
1	.....	.....	0.2	+ 9 days. Cult. +	0.2	Lived.
2	.....	.....	....	.....	0.1	"
3	.....	.....	....	.....	0.1	"
4	.....	.....	....	.....	0.06	"
5	.....	.....	....	.....	0.02	"
6	0.01	+ 11 days. Cult. +	0.02	Lived.	0.01	"
7	0.001	+ 5 days. Cult. +	0.002	+ 13 days. Cult. +	0.002	"
8	0.0001	Lived.	0.0002	+ 10 days. Cult. 0	.....	.....
9	0.00001	"	0.00002	Lived.	.....	.....
10	0.000001	+ 17 days. Cult. +	0.000002	"	.....	.....

The virulence of the strain was such that 0.001 cc. of a 24-hour serum-broth culture was the minimal dose which was certainly fatal for guinea-pigs. In several other series of guinea-pigs, injected to determine the virulence of this strain, doses of 0.001 cc., or less, were almost invariably fatal. Much smaller doses, even 0.000001 cc., were often fatal, but not regularly so. The animals which died showed a septicæmia at autopsy, but usually the number of organisms present in the blood was not large. The minimal fatal dose for mice and rabbits varied from 0.000001 cc. to 0.0000001 cc.

The survival of the sensitized pig, B No. 5, which received 0.02 cc., of a living culture is to be regarded as a definite indication of immunity, since no normal animal survived one-tenth as large a dose. But that such sensitization does not produce regularly any noteworthy immunity is shown by the death of two animals in the series which received smaller doses of the culture. The regularly "immunized" animals in series C were much more resistant, surviving 100 and 200 times the M. L. D. However, of the 32 animals in which immunization was attempted about three-fourths died in the process, and the

seven survivors in series C probably possessed an unusually high degree of natural resistance.

To test for hypersensitiveness, three of these immunized animals were given an intravenous injection of extract of pneumococci 4 weeks after the last injection of living culture.

TABLE IX.—REACTIONS OF IMMUNIZED AND SENSITIZED PIGS TO PNEUMOCOCCUS EXTRACTS.

No. of animal.	Wt. in gms.	Previous treatment.	Wt. in gms. of culture = x. tract per 250 gms. of guinea-pig.	Duration of extraction.	How heated.	Result.		
						Reaction.	Outcome.	Autopsy.
110	300	None.	0.060	18 hrs. 37° C.	1 hr. 60° C.	0	Lived.	.....
111	350	"	0.060	" "	" "	0	"	.....
159	480	"Sensitized."	0.040	" "	1 hr. 55° C.	++	+ 5 min.	Typical.
160	480	"Sensitized."	0.040	" "	" "	++	" "	"
C., No. 3. 183	500	"Immunized."	0.060	" "	1 hr. 60° C.	++	" "	"
C., No. 5. 53	330	"Immunized."	0.060	" "	" "	++	" "	"
C., No. 2. 180	530	"Immunized."	0.060	" "	" "	++	Lived.	.....

This table shows that Nos. 159 and 160 were highly sensitized. They had received the same preliminary injections of pneumococci to cause sensitization as had the animals of series B in Table VIII. It also shows that, with the higher grade of immunity produced by a series of injections of small doses of living, virulent pneumococci, a marked degree of hypersensitiveness to pneumococcus protein also developed. But that there is any direct causal relationship between these conditions, is not demonstrated by these experiments.

As is well known, in man a tuberculous infection often results in the development of marked hypersensitiveness to tuberculin. This is demonstrable in several ways, but is most simply and conveniently shown by direct application of the diluted tuberculin to the conjunctiva, as in the ophthalmic test of Calmette; or to the skin, as in the cutaneous test of von Pirquet, or on intracutaneous injection. Solutions which cause no symptoms in normal individuals, may cause a marked inflammatory local reaction in the hypersensitive tuberculous patient. The evidence is strongly in favor of the view that this local condition of hypersensitiveness is associated with, and due to, a general hypersensitiveness to tuberculo-protein. The evidence for this view has been well summarized by Hamman and Wolman.[11]

In this work, attempts were made to demonstrate in man an analogous condition of hypersensitiveness to pneumococcus protein by instillations into the conjunctiva, and by intracutaneous injections. As these preliminary tests were unsuccessful, no attempt was made to demonstrate such a possible hypersensitiveness by transferring it passively to guinea-pigs, by injections of the patient's blood or serum. There seemed no prospect of success, in view of the fact that a similar passive transfer to guinea-pigs of hypersensitiveness to tuberculo-protein in man, is very rarely demonstrable,[12] although marked local reactions of the skin and conjunctiva in man are frequently obtained.

A protein precipitate, the activity of which had been demonstrated by its power to intoxicate sensitized guinea-pigs (see Table III), was dissolved in physiological salt solution, to form a 1 per cent solution; and heated 1 hour at 60° C. If suitable, it dissolved readily and formed a slightly opalescent, colorless solution. If dark in color, or turbid, it was centrifugalized till clear and reprecipitated. Filtration through a Berkefeld filter was avoided because it was thought that the activity of the material might be lessened in the process. A small quantity of the solution was instilled into the eyes of several normal and sensitized guinea-pigs, and also into the eyes of several normal and immunized rabbits. Subcutaneous and intracutaneous injections were also made. As the solution was found to be quite harmless to these animals, it was employed on patients. After being dissolved, the material was kept on ice over night, before use on patients; but it was never used, if more than 24 hours old.

An eye test was made by instilling a drop of a 1 per cent solution into the conjunctival sac of one eye. The usual precautions taken in carrying out a Calmette reaction were observed. The eyes were examined and carefully compared several times during the following 36 hours.

In all, there were tested 15 patients with pneumonia and, as controls, 20 patients, suffering from a variety of other conditions. In 2 of the former 15, tested at or near the crisis, there developed reactions of moderate severity. In from 4 to 6 hours there appeared a moderate fibrino-purulent discharge, with definite congestion of the palpebral conjunctiva and caruncle, and some dilatation of the bulbar vessels. There was some lacrymation, and slight discomfort. The difference in appearance of the two eyes persisted for 24 hours.

In 4 other patients with pneumonia there developed a slight, but definite, congestion of the caruncle and palpebral conjunctiva of the eye tested, with a small amount of exudate. In 1 control, a colored man with tuberculous peritonitis, a similar reaction was obtained. These mild reactions all subsided within 24 hours. The other 9 patients with pneumonia and the 19 controls gave no reactions.

A cutaneous reaction was also tried in 7 cases of pneumonia and in a number of control patients. In some cases the skin was scarified, as for a von Pirquet reaction, and a drop of a 1 per cent solution of the protein applied and allowed to dry.

In all of these 7 cases intracutaneous injections were made of 0.05 cc. of a 1/10 to 1/100 per cent solution of protein. The injection of this amount of a 1 per cent, or a 1/4 per cent solution in man caused painful inflammatory reactions that subsided after 24 hours, although they caused no reaction in guinea-pigs or rabbits. The injection of the more dilute solutions caused milder reactions that were but little, if any, more outspoken in the patients with pneumonia than in the control patients. A discrete papule usually developed, 0.5 to 2.0 cm. in diameter, surrounded by an ill-defined area of hyperæmia. It was usually but slightly elevated. In some cases there was a more diffuse swelling of the surrounding tissues. Although actual measurements of the papules averaged a little larger in pneumonia patients than in the control cases, the difference

was slight and not constant. There was no difference in the reaction at different stages in the disease, either early in the acute stage, at the crisis, or late in convalescence.

SUMMARY.

By means of a slight modification of Besredka's method, a "protein" extract was obtained from pneumococci which would sensitize normal guinea-pigs, and which would specifically intoxicate suitably sensitized guinea-pigs. But it was not found possible to prepare extracts in this way which uniformly caused acute fatal reactions in sensitized animals.

During the process of extraction, as pointed out by Rosenow, a certain degree of autolysis apparently occurs, which causes the extract to acquire a considerable degree of toxicity, if the extraction is too prolonged. Heating one hour at 60° C. greatly reduces the toxicity, but does not always entirely destroy it. Normal animals, which die from the intravenous injection of such toxic extracts, show practically the same symptoms, and the same findings at autopsy, as do animals that die in typical anaphylactic shock.

There is quantitatively a certain degree of specificity in the reactions of suitably sensitized animals to extracts of pneumococcus and *Str. viridans;* probably also in reactions to these extracts and to extracts of *Str. pyogenes;* but this specificity is not absolute.

Guinea-pigs sensitized with extracts of pneumococci showed inconstantly a very slight grade of immunity to infection with living, virulent cultures. Animals highly immunized by repeated subcutaneous injections of living, virulent cultures, showed also a marked degree of hypersensitiveness to pneumococcus extracts.

It was not possible to demonstrate a condition of hypersensitiveness to pneumococcus "protein," in patients with pneumonia, by the local application of a solution of the protein to the conjunctiva or by intracutaneous injections.

In conclusion I wish to thank Dr. Lewellys F. Barker for permission to carry out and report this work, and for his constant encouragement and advice.

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IN MEMORIAM.

JAMES G. MUMFORD.

The Johns Hopkins Hospital Medical Society desires to place upon record its appreciation of the life and work of Dr. James G. Mumford, who died at Clifton Springs, New York, October 18, 1914. Upon different occasions, Dr. Mumford has honored this society by presenting papers on various topics and always of unusual interest and merit. This is true also of The Johns Hopkins Hospital Historical Society. Dr. Mumford was a many-sided man. As a surgeon, he early achieved distinction in his chosen profession, where, among other characteristics, his sound judgment and keen perception were especially noteworthy. As an author and historian, his clarity of diction and elegance of expression, together with accuracy of statement and sterling honesty of purpose, combined to place his writings far above the ordinary. As a friend and companion, it would be difficult to find a more charming and winsome personality, always affable, courteous and tolerant of the opinions of others, yet firmly tenacious of principle and ever ready to defend the right as he saw it. His indomitable courage and unfailing cheerfulness, in the face of ill health and enforced retirement from the active practice of surgery, were an inspiration to those who knew him. Therefore, be it

Resolved, That in the untimely death of Dr. James Gregory Mumford, the medical profession has lost one of its ablest and most productive members, and that we, as a society, have lost an honored and trusted friend. And be it further

Resolved, That a copy of these resolutions be spread upon the minutes of this society, be printed in THE JOHNS HOPKINS HOSPITAL BULLETIN and be sent to Mrs. Mumford.

HENRY B. JACOBS,
J. M. T. FINNEY,
Committee.

THE RECOGNITION OF ATYPICAL FORMS OF INTESTINAL AMŒBIASIS.*

By ANDREW WATSON SELLARDS

AND

WALTER ALBERT BAETJER.

(From the Medical Clinic of the Johns Hopkins Hospital.)

OUTLINE.

I. Introduction:
  1. Frequency of diarrhœas of obscure origin.
  2. Lack of variation in the classical picture of amœbic dysentery.

II. Clinical description of these obscure cases:
  1. General type of case.
  2. Contrasts between these and cases of amœbic dysentery;
    A. Continuous course of symptoms,
    B. Mildness of symptoms,
    C. Character of stool,
    D. Lack of response to emetine,
    E. Absence of characteristic amœbæ in the stools.
  3. Occasional points of similarity.

III. Investigation of the ætiology of three cases of diarrhœa:
  1. Essential features of the clinical examination of these patients.
  2. Investigation of the amœbæ occurring in these cases;
    A. Morphology,
    B. Pathogenesis,
      a. Clinical effect in animals,
      b. Morphology of the amœbæ in animals,
      c. Pathologic lesions in animals.

IV. Relationship of various strains and species of amœbæ:
  1. *E. histolytica*,
  2. *E. coli*,
  3. *E. limax*,
  4. Unidentified strains.

Introduction.—In the past few years there have come to light some rather surprising instances of the confusion between parasitic and non-parasitic diseases. Ordinarily, the clinical symptoms of these two groups of conditions are sufficiently distinct to differentiate them sharply, but cases have been encountered in which the distinction, based upon clinical grounds alone, was erroneous, as in infantile paralysis and in the metabolic types of peripheral multiple neuritis such as the predominant form of beri-beri. In some conditions, notably in dermatology, difficulty arises in the distinction between parasitic and metabolic conditions because of the comparatively mild nature of the disease and the absence of any outspoken distinctive symptoms. A similar confusion suggests itself in certain diarrhœal diseases in man, in view of the comparative mildness of the symptoms and the manifold causes that must be considered.

In the present paper we shall consider the ætiology of some obscure cases of dysentery and diarrhœa occurring here in Baltimore during the past winter. Our attention has been directed especially toward three cases which represent fairly distinct types of conditions. One of these patients (A) was a negro from the West Indies. He gave a history of a luetic infection; the blood serum gave a positive complement fixation with luetic antigen and proctoscopic examination showed the findings characteristic of a syphilitic proctitis. A continuous diarrhœa had been present for some years. These findings led to the conclusion that the diarrhœa was due to the anatomic changes occurring in the mucosa of the sigmoid and rectum, resulting from the syphilitic infection. The second patient (B) was a boy of 14 years, who presented the anatomic conditions of Hirschsprung's disease accompanied by a diarrhœa of long standing. This latter symptom was interpreted as the result of the extensive dilatation and the loss of function of the bowel incident to the development of a giant colon. The third case (C) was one of distinctly atypical amœbic infection.*

In the consideration of the ætiology of an obscure diarrhœa, perhaps the first distinction to make is the differentiation between the parasitic group and those of non-parasitic origin, such as occur in the condition of achylia gastrica, or those conditions like the case of Hirschsprung's disease, just mentioned, where the anatomic condition would presumably account for the diarrhœa. We have been interested especially in those patients in whom the possibility of amœbic infection is to be considered.

The symptoms of amœbic dysentery in man are remarkably constant, there being comparatively little variation in the classical picture. The disease is indeed a far from simple one, inasmuch as it is often accompanied by many complications. Moreover, the differences between the acute and chronic types are often very sharp. A third group of cases has been described by Strong[1] in which the symptoms are comparatively mild. Slight prodromal disturbances may exist for several months, the condition terminating eventually either in recovery or in a frank typical dysentery. It will be seen that this condition is essentially different from that of a persistent watery diarrhœa.

Apparently all cases of amœbic infection, when well established, conform to the usual picture of either the acute or chronic stage. Even in heavily infected endemic zones, one finds little evidence of atypical or unusual cases. Thus, so far, no success has been attained in the attempt to attribute an amœbic ætiology to hill diarrhœa, such as occurs in India or in the summer capital of the Philippines in the Benguet Mountains and other hill stations of Asia. Indeed, it would seem that, like other longstanding protozoan infections, such as

* Presented at the eleventh annual meeting of the American Society of Tropical Medicine, held in Boston, May 29, 30, 1914.

* This patient was seen through the kindness of Dr. Earle and Dr. Sexton of the visiting and resident staff of the Hebrew Hospital.

malaria and trypanosomiasis, the symptoms of amœbic infection remain remarkably constant. But in looking for unusual chronic types of infection, it is conceivable that these might occur, not primarily in the tropics, where the optimal conditions prevail for the development and propagation of the disease, but rather in the north, where the disease must maintain itself under unusual and adverse conditions. Accordingly, we have examined some of the atypical cases of diarrhœa in various ways in order to detect, if possible, unusual examples of amœbic infection.

Clinical Description of Obscure Diarrhœas.—In those cases of diarrhœa which came under observation, there were certain general features which were characteristic of the group, though, of course, the symptoms of the individual patients varied among themselves. For the most part, the general health of the patient was comparatively good and the principal symptom was the annoyance of frequent stools. The disease, when once established, ran a continuous course over a period of several years, free from any intermission or remission of symptoms. The stools were usually frequent, containing much water, but little or no mucus and blood. Microscopical examination of these cases sometimes showed amœbæ, but the characteristic *Entamœba histolytica* was absent. Moreover, the amœbæ in these cases did not disappear after injections of emetine; neither did the symptoms yield to this therapy. Such cases present a marked contrast to the typical chronic cases of amœbic dysentery, in which periods of apparent health alternate with acute relapses, the relapse being characterized by the appearance of bloody mucous stools rich in amœbæ, but the parasites and symptoms disappearing temporarily, either spontaneously or upon the injection of emetine. In view of the relative constancy of the essential features of chronic amœbic dysentary, it would seem that there is little ground for any correlation of these cases of diarrhœa with amœbic infection. In the details of the histories of these patients, there are but few points of similarity in common with amœbic dysentery. Perhaps it is significant, though, that the symptoms were of several years' duration in two of these patients and in the early days of the disease at least a definite dysentery had existed; while one of these patients was under observation, periods frequently occurred in which a considerable quantity of blood appeared in the stools, but in the intervals between these hemorrhages, the watery diarrhœa continued.

Considerations in Regard to the Diagnosis of Amœbic Dysentery.—In considering the interpretation to be placed upon the occasional appearance of amœbæ in these cases, it is necessary to discuss briefly the basis on which it is permissible to diagnose amœbic dysentery and the significance of the occurrence of amœbæ in the intestinal tract. For the present we feel that it is necessary to accept the view that *there are but two parasitic amœbæ of man, one of which, E. histolytica, is pathogenic, and the other, E. coli, though parasitic, is non-pathogenic.* In order to make a diagnosis of amœbic dysentery the clinical symptoms must be present, and it is also necessary to demonstrate the presence of *E. histolytica*, though, for practical purposes, one is perfectly safe in diagnosing dysentery when a patient is passing bloody mucous stools, containing numerous active amœbæ.* Hypothetically one would have to guard against the occurrence of a bloody, mucous dysentery of neither bacillary nor amœbic origin in a patient already harboring *E. coli;* but, in such a condition, the conservative course, from a clinical standpoint, would be to use emetine therapy. Furthermore, mixed infections with the two species of entamœbæ are so common that the presence of *E. coli* in a case of dysentery would in no sense militate against the simultaneous occurrence of *E. histolytica*, even though it could not be demonstrated microscopically at all times. However, as in many bacterial conditions, comparatively little reliance can be placed upon the establishment of the presence of pathogenic entamœbæ in the intestine without considering also the clinical condition of the patient. Unlike what occurs in trypanosomiasis and malaria, such perfectly typical carriers[2] develop that the occurrence of *E. histolytica* in the stools does not necessarily prove the presence of any diseased condition. Indeed, in addition to the carriers resulting from a typical attack of dysentery, individuals are sometimes found with virulent four-nucleated cysts of *E. histolytica* in the stools, who, as far as they know, have never had any symptoms of dysentery.[3] The diagnosis, therefore, is extremely easy in a typical case during an acute attack. However, when only indefinite symptoms occur accompanied by the presence of amœbæ in the stools, then it becomes much more important to identify the species absolutely. In cases where only a mild diarrhœa exists and where only an occasional amœba is found in the stools, which cannot be identified with *E. histolytica*, then the diagnosis of amœbic dysentery would not be justified, especially where other causes of diarrhœa are present. We have studied such cases as this during the winter of 1913-14, to determine, if possible, the ætiologic factor involved. This has been approached by examining these patients for various conditions that might be responsible for the diarrhœa, and by studying the amœbæ occurring in these cases, especially with regard to their identity as determined by their morphology and their pathogenicity for animals.

Identification of the Parasitic Amœbæ.—The identification of the two parasitic species of amœbæ which may occur in the human intestine cannot be determined by animal inoculation, even though the one species is pathogenic and the other harmless, on account of the frequency of mixed infection with both species, and the uncertainty of animal inoculations. Thus, the pathogenic species may fail to produce dysentery upon inoculation, and it is always possible that a stool in which the nonpathogenic species predominates may produce dysentery on account of the presence of a few pathogenic forms that have

* We have used the term amœbæ in a very general sense, applying it to the parasitic, as well as free-living amœbæ; for certainly, in a vernacular sense, the entamœbæ belong to the larger group of amœbæ. In cases where the distinction between the free-living and parasitic forms is not perfectly clear from the context, the term entamœbæ has been used. It is certainly necessary to have a term which may be applied to either the free-living or the parasitic group, especially in discussing a form of which the identity has not been established.

been overlooked microscopically. Accordingly the distinction must be made by the differences in the morphology of the two species. In typical dysentery from *E. histolytica* and in normal individuals carrying *E. coli* it is comparatively easy to recognize the morphological differences which have been described in the two types of trophozoites. But in chronic cases, which are healing, in which there is comparatively little blood and mucus for the amœbæ to feed upon, and in which the bowel is approaching its normal condition, Walker[3] has pointed out that the trophozoites of *E. histolytica* approach those of *E. coli* in their morphology and the distinction between them becomes much more difficult. Indeed, it may be necessary to see the propagative stage in order to determine whether the cysts contain the classical number of four nuclei or eight, before we can identify the species. These observations are of especial importance in our own cases, since we were dealing with such chronic types. Accordingly, in addition to the study of the trophozoites, we have taken precautions to secure stained specimens of the propagative stage as well. In testing the pathogenicity of these amœbæ, upon animal inoculation, it seemed advisable to take special precautions, in view of the mildness of the symptoms and the scarcity of the organisms in these cases. Accordingly, we have depended largely upon the technique of exposing the cæcum under general anæsthesia and inoculating directly into the lumen against the mucosa of the bowel.

Etiology of These Diarrhœas of Obscure Origin.—For a thorough analysis of the symptoms presented by these patients, the following details of their records are helpful:

CASE A.—This patient, aged 40, a negro from the Cape Verde Islands, had had two diseases in the past that are important in connection with his present condition. About 15 or 20 years ago he contracted syphilis and apparently received but little treatment. About 10 or 12 years ago, while in Egypt, he contracted a typical bloody mucous dysentery. The exact details of these early symptoms are forgotten, but apparently intermissions in the symptoms occurred during the early years of the disease, such as are typical of the amœbic form of dysentery. In the past few years, however, there had been no intermission in the symptoms with periods of apparent health, such as one expects to find in amœbic infection. The patient gave a history of passing as many as twenty stools per day. These were very watery, and contained practically no mucus, and no blood except for occasional bleeding from some external and internal hæmorrhoids.

Physical Examination.—The patient was somewhat undernourished. The cardiovascular system was normal except for fairly well-marked atherosclerosis. The abdomen was slightly tense and also somewhat tender on deep palpation, especially near the median line below the umbilicus. The thickened sigmoid was readily palpable. Proctoscopic examination showed a very marked proctitis with ulcerations of the mucous membrane, which bled readily and were covered with a purulent discharge. In some areas the induration of old scars could be seen. The condition suggested very definitely a luetic proctitis. The blood serum gave a positive Wassermann reaction. Examination of the stools for parasites, after purging, showed numerous flagellata, and an occasional small, sluggish amœba. Cultures for *B. dysenteriæ* were negative.

From these data it is seen that the picture was a somewhat complicated one, but the weight of evidence seemed to indicate definitely that the symptoms then present ought to be ascribed to a luetic proctitis. The patient was given 0.6 gm. of salvarsan intravenously. Within three days the number of stools decreased from about 10 to one or two per day, the flagellates diminished markedly in number, and the amœbæ disappeared completely. Within 10 days after the injection of salvarsan, however, the number of stools gradually increased to five or six per day, the flagellates returned, and occasionally the trophozoite of an amœba was found. Injections of emetine in doses of ⅔ of a grain daily, for eight days, failed to control the diarrhœa. The vegetative amœbæ disappeared from the stool, but cyst-like bodies were constantly present.

CASE B.—The second case was that of a school boy, aged 14, who came to the hospital, in December, 1913, complaining of pain in the stomach and diarrhœa. About 9½ years ago the patient contracted a diarrhœa of gradual onset lasting only a few weeks, and assumed to be only "summer complaint." This diarrhœa returned in the following summer, three to five stools being passed in the 24 hours, with an occasional discharge of blood during the first few weeks after the return of symptoms. It has persisted almost continuously since that time, principally as a watery diarrhœa. During the past year the patient has had dull pains in the stomach, especially after meals, and the "stomach" began to grow to a relatively enormous size. Recently the patient has been losing weight and becomes tired very easily.

Physical Examination.—The patient was a sparely nourished, frail-looking boy, distinctly sallow and small for his age. The temperature ranged from 100° to 101° F., with a leucocyte count of 6000. The lungs were normal except in the left interscapular region, where there was broncho-vesicular breathing. The Calmette reaction with tuberculin was negative. The abdomen was markedly and rather uniformly distended, with the costal margins flared out, the iliac grooves practically obliterated and the lumbar curves bulging slightly. The sigmoid was readily palpable, but the enlargement appeared to be due chiefly to the dilatation of the colon. The X-ray examination showed a redundant sigmoid with spastic dilatation of the remaining colon, suggesting a true obstruction, such as would be caused by a fibrous band just above the sigmoid. These findings led to the diagnosis of Hirschsprung's disease with the possibility that a chronic inflammatory process, such as tuberculosis, was superimposed on this condition.

An examination of the stools showed the presence of red blood cells, numerous flagellata, and a few non-motile trophozoites of amœbæ. In the third week after admission to the hospital this boy complained of acute cramps in the abdomen. The stools at this time were copious and contained moderately large amounts of fresh blood. On microscopic examination, moderate numbers of sluggishly motile amœbæ were found.

Inasmuch as these chronic cases yielded very poorly indeed to either emetine or ipecac therapy, we used a decoction of chaparro amargosa as recommended by Nixon.[4] In the course of a week, however, it was found necessary to discontinue it on account of the nausea that developed. Even in this length of time, however, the flagellata and amœbæ diminished definitely in numbers and the amount of hæmorrhage from the bowel was markedly reduced. For further treatment, surgical interference was decided upon and the patient was transferred to the surgical service of this hospital. An appendectomy and a cæcostomy were performed. In addition to the enlargement of the cæcum and colon, a condition of adiposis epiploicæ was found, the pelvis being practically filled with fat. Irrigations with quinine solutions were carried out, beginning with 1:5000 and increasing to 1:750 within six weeks; and this strength was continued for a period of three weeks. During this time the symptoms improved considerably. The stools, though still unformed, were distinctly less watery and contained only traces of blood. On microscopical examination it was found that the flagellata had disappeared entirely and only a few cysts of amœbæ were present.

Case C.—The third case was somewhat different from either of these. The patient did not give a definite history of amœbic dysentery at any time in the past, but attacks of diarrhœa had occurred frequently. This symptom had been constantly present for the past 18 months and had proven very refractory to therapy. When first seen by Dr. Earle and Dr. Sexton, vegetative amœbæ were present in the stool, but their morphology was not sufficiently characteristic to permit of identification. A few days later, on proctoscopic examination, several discrete ulcers with rolled edges were seen in the mucosa of the rectum. Scrapings from these contained cyst-like bodies with two and three nuclei, but neither trophozoites nor four-nucleated cysts were found. This patient was treated with emetine in one-grain doses for about one week, and with ipecac in 80-grain quantities on two successive nights, but with comparatively little benefit.

Investigation of the Amœbæ in These Cases.—The amœbæ found in these cases were studied in several ways to determine whether they bore any ætiologic relationship to the symptoms occurring in these patients. First of all, the morphology was studied, both in the vegetative and propagative phases. In one case (A) a series of cultures was made on a special agar-agar to test for the presence of the limax group. The tests for pathogenicity were carried out by the inoculation of kittens. Inasmuch as case A was, in many respects, the most important of these three, it will be discussed first.

Morphological Characteristics.—The examination of fresh preparations of the stool of this patient showed numerous flagellata and an occasional amœba. It was evident that the flagellates might, in part, be responsible for the continuance of this diarrhœa once it had been inaugurated, but it did not seem that the amœbæ present could be playing any very active part. In the first place, they were extremely scarce, the trophozoites appearing only after the administration of salts, a condition often occurring in the infection of normal individuals with the harmless *E. coli*. In the unstained preparations the amœbæ were rather small in size and very sluggishly motile. the cytoplasm was somewhat hyaline in appearance and, correlated with the sluggish motility: the ectosarc and endosarc were not differentiated. The amœbæ were also free from red blood cells inasmuch as there was no bleeding from the mucosa. The nucleus could be seen rather easily and tended often to occupy a somewhat concentric position; on staining * its characteristics were not typically those of either *E. coli* or *E. histolytica*. The nucleus was distinctly richer in chromatin than in either of these species, and it was arranged in rather large irregular masses.

A search for the propagative stage revealed many cyst-like bodies containing one, two, and three nuclei, but after examining five preparations, we found only one of these bodies with four nuclei. In view of these rather gross differences it did not seem necessary to make an elaborate comparison of the finer details of structures in these various strains at this time. The general characteristics of these strains suggested some of the degenerative types which have occasionally been described as distinct species, such as the *E. minuta* of Elmassian (1909), which is probably a strain of *E. histolytica;* or the *E. nipponica* of Koidzumi (1909). This amœba was classified originally by Walker [3] as an aberrant form of *E. coli,* and by Hartmann [4] as a degenerated form resulting from the deterioration of either *E. coli* or *E. histolytica*. It was evident, from a microscopic examination of their morphology, that these amœbæ could not be placed definitely in either the histolytica or coli group. The general characteristics of the amœbæ seen in this case, therefore, in connection with the clinical findings, does not justify a diagnosis of amœbic dysentery. An ætiologic rôle could be ascribed to these amœbæ only if it could be clearly proven that they possessed definite pathogenic properties. On the other hand, it is necessary to exclude the possibility that these forms may be a saprophytic species.

Attempts at Cultivation.—On account of the comparative richness of the nucleus of some of the forms in chromatin and the frequency of uninucleated cysts, it seemed advisable to rule out the possible presence of some of the limax group. Some evidence has accumulated which suggests that, under favorable conditions, members of the limax type may not only pass through the intestine mechanically, when ingested with food, but that they may even colonize temporarily. Ordinarily, the occurrence of even a few trophozoites in the fæces is acceptable evidence that the form in question is not one of the free-living species. In order to exclude it rigidly, however, cultures were made, at intervals of two or three days, over a period of one month. These cultures were made as a routine on an agar medium based on Musgrave and Clegg's [6] work. Since the amount of alkali used in this medium may exert a pronounced influence, we used, not only 2 per cent of normal sodium hydroxide, but varying quantities, from none to 2 per cent. Duplicate cultures were sometimes made by inoculating highly diluted broth, dextrose solutions, and even distilled water, with varying amounts of fæces, since under special conditions these fluid media occasionally give very good results. These solid and fluid media were prepared according to the technique used in previous work with cultures of free-living amœbæ.[7] The results were constantly negative at all times on the various media. Suitable controls were carried out to demonstrate the efficiency of the agar media for the cultivation of the limax group. These consisted in the inoculation of agar tubes with a culture of limax, isolated originally from a case of amœbic dysentery, in the recovery of this culture from the stools after injection into animals, and also by demonstration, by cultural methods, of two species of the limax group occurring spontaneously in a normal kitten. These two species had not colonized, but evidently had been ingested with food

* For the staining technique see Baetjer and Sellards, Bull. Johns Hopkins Hosp., 1914, XXV, 165.

In the illustrations in the following plates, it will be noticed that frequently the nucleus is relatively large compared with the size of the cell. This characteristic increases the difficulty which sometimes arises in distinguishing, in stained preparations, between the cells of the host and the amœbæ. In order to control this, we have studied various materials stained with hæmatoxylin in the same way as the amœbæ. Pus cells from several sources were examined in view of their possible confusion with cysts. In addition to some smears of normal mucosa, preparations were made at varying intervals from mucosa which was allowed to digest in the thermostat, in order to secure examples of the slightly amœboid metazoan cells.

and were passing through the bowel mechanically, for the stool was entirely negative for cysts and trophozoites on microscopic examination, and after two days the cultures became negative for amœbæ.

The details of the control experiments of the animals injected were as follows: Two half-grown kittens were purged and examined for amœbæ, but no cysts nor trophozoites were found. Cultures on amœbæ agar remained free from amœbæ. On the next day each animal was injected, directly into the cæcum, with a suspension in 0.2 per cent salt solution of the growth of three agar slants of a culture of a limax amœba, containing an abundance of trophozoites and cysts, a culture being used which was known to be capable of passing mechanically through the alimentary tract of man.[3] Specimens of stools, obtained with a rectal tube, were examined each day for a week, both microscopically and culturally. No trophozoites nor cysts were seen at any time. The amœbæ were readily recovered on agar plates from both animals during the first four days after the injection. The plates on the fifth and sixth days remained free from amœbæ. This period of four days is certainly not longer than would be required for the intestinal tract to free itself mechanically from the large quantity of the culture which was injected; and the absence of amœbæ on microscopical examination is good evidence that no colonization took place. This behavior of these amœbæ in kittens corresponds exactly to their behavior in man. One of these kittens was sacrificed on the sixth day. No inflammation of the bowel was present, the mucosa being entirely normal. Cultures and microscopic preparations from the mucosa and the intestinal contents of the colon were entirely negative for amœbæ. The second cat was kept under observation for two months, but developed no clinical symptoms whatever. The cultivation of the limax amœbæ from the stools, especially in the case in which two species occurred spontaneously, is sufficient evidence that a satisfactory technique was used. In view of the repeatedly negative results obtained over a long period in the attempt at cultivation, it is evident that the amœbæ seen on microscopical examination were not members of the limax group.

Determinations of Pathogenesis.—One of the cardinal points in the examination of the strains of amœbæ occurring in these patients is the determination of their pathogenesis. In view of the high percentage of failures upon inoculation of virulent *E. histolytica* into kittens, it seemed very unlikely that the few atypical forms occurring in this patient would produce any effect. Nevertheless, since *E. coli* can colonize in kittens, it was evidently desirable to determine the fate of these amœbæ after inoculation. Accordingly, a kitten about one-third grown was selected for inoculation; microscopic examination of stool specimens obtained with the high rectal tube and by purgation with magnesium sulphate showed no form of protozoa. The injections were then made in three places; namely, into the cæcum, into the ileum about one foot above the ileocæcal valve, and into the stomach, a total of 6 cc. being used in each location. The specimen used for inoculation was rich in flagellates, but contained not more than one or two vegetative amœbæ in a coverslip preparation, and no four-nuclear cysts, though cyst-like bodies with one, two, and three nuclei were abundant. Frequent examinations of the stools were made during the next few weeks, but no amœbæ nor flagellates were found and no clinical symptoms appeared. In the fifth week, however, one month after inoculation, frequent unformed stools were passed and these contained a few motile amœbæ. Examination, after salts, showed moderately large numbers of amœbæ, but no flagellates in either the active or encysted stage. Moreover, the amœbæ, though moderately abundant, were never excessively numerous, as in typical dysentery in man and animals. Cultures for the limax group remained entirely negative. The diarrhœa continued, the stools gradually becoming somewhat more watery and rather more frequent. The stools were free from blood and mucus, however, and tests for blood with guaiac were negative. Bacteræmia, which was found to accompany infections with typical histolytica almost constantly in young kittens,[2] did not develop in this animal; on the contrary, its general health was unimpaired and its growth continued rapidly. The amœbæ occurring in this animal were slightly larger and more active than those seen in the patient, there being some differentiation between ectosarc and endosarc. On staining, the nucleus was poorer in chromatin, as compared with some of the forms seen in the patient, but it was still distinctly richer than is the case with *E. histolytica* and *E. coli*. The impression obtained from observation of the trophozoites was that their resemblance to the histolytica type had increased after a single passage in animals. This change was seen not only in the nucleus, but also in the larger size of the organisms, their increased mobility, and the slight differentiation between ectosarc and endosarc. Changes of even greater significance occurred in the propagative stage. Cysts with four nuclei were not very uncommon and occasionally as many as five or six nuclei were found. In the cysts occurring in the patient, it will be remembered that four nuclei was the absolute maximum, the predominant numbers being two and three.

After the symptoms had persisted for two months, the diarrhœa began to diminish slightly and the amœbæ became somewhat less numerous. No blood appeared microscopically, but at times after extraction of the acidified stool with ether, a positive reaction was obtained with guaiac. At this stage the animal was sacrificed. The large bowel showed a few small hyperæmic areas, but no definite lesions were present. Moderate numbers of amœbæ were found and these were used for the intracæcal injection of two young kittens. The incubation period in one was five and in the other 10 days, though it must be noted that the material used for inoculation was much richer in amœbæ than in the first transfer from the patient. In the second passage mucus was occasionally present. No blood was seen except on microscopic examination, but the guaiac test for blood in the ether extract of the stool was positive. The kitten showing an incubation period of five days died on the following night, though presumably not from the amœbic infection, but from some unknown cause. At autopsy the large bowel showed a moderate degree of hyperæmia in some areas, but no other changes. Amœbæ were fairly abundant in the contents of the

bowel. They were not very well preserved, but apparently approached the histolytica type. The second animal died at the end of the third week after inoculation. The small bowel was intensely injected in the lower half of the ileum, the hyperæmia ending sharply at the ileocæcal valve. The contents of the large bowel were sero-purulent and contained many amœbæ. There was, however, no definite ulceration of the large bowel. The amœbæ were smaller in size than the usual parasitic forms, but they definitely resembled the histolytica type more closely than the forms originally seen in the patient. Inoculations were made from this animal into two kittens, one being inoculated by rectal tube, and the other intracæcally.

The animal inoculated by rectal tube died four days later. At autopsy there were no signs of amœbic infection. The animal inoculated intracæcally died on the third day of peritonitis. The stools, however, contained active amœbæ and the mucosa over the lower half of the rectum showed well-marked diffuse injection. Stained preparations of the amœbæ were not obtained during life and at autopsy they were not sufficiently well preserved to permit careful study.

In the second case (B) the amœbæ were somewhat intermediate between the coli and histolytica types, but here also the comparative richness of the nucleus in chromatin would not permit of a definite diagnosis of *E. histolytica*. Inoculations were made into a kitten during one of the periods when the patient was passing a considerable amount of blood. After an incubation period of three days a sharp attack of dysentery occurred, characterized by copious stools containing numerous flecks of blood and mucus with numerous amœbæ. This attack ended promptly in recovery before any entirely satisfactory specimens were obtained for morphological study.

The third case was rather different from these two, in that we were not able to find any trophozoites in the period during which this case was under observation. Material from the scrapings of the ulcers was comparatively rich in cyst-like bodies containing from one to three nuclei, but no four-nucleated forms were found. A kitten was inoculated with this material into the cæcum and into the stomach. After an incubation period of one month, a watery diarrhœa developed, corresponding to that seen in the patient. The amœbæ were fairly abundant, especially after purging. They did not differ essentially in morphology from those seen in the first transfer from the first patient (A). Since no trophozoites from this patient (C) were available for comparison with those in the subpassages, this strain was not carried any further. The symptoms in this kitten persisted continuously for about one and a half months and then became very much milder. After two months the animal was sacrificed; no evidences of amœbic infection could be found, either in the anatomical or microscopic examination of the bowel.

The results of these animal inoculations are significant, both in the interpretation of the ætiologic relationship of the amœbæ to the symptoms of these patients, and also in the determination of the relationship of these strains of amœbæ to the two parasitic forms in man. It is evident that the amœbæ occurring in these cases are pathogenic for kittens. The duplication of the characteristic symptoms of the patient in kittens and the exclusion of other adequate causes of diarrhœa justify the conclusion that the amœbæ were the ætiologic factor in producing the symptoms seen in these patients. This conclusion is especially clear, since the flagellata, present in great abundance in two of these patients, did not even colonize when inoculated into kittens.

Comparison of Various Species of Amœbæ.—The identity of the amœbæ occurring in these atypical cases, however, is not entirely clear. Accordingly, we have compared them in their morphology and pathogenesis with the better-known types; namely, *E. histolytica*, *E. coli*, and one member of the *limax* group. The strain of histolytica was obtained during an acute relapse in a typical chronic case from North Carolina. Examples of *E. coli*, for morphological study, were obtained from a cardiac case in a boy of 19, who had never been south of Maryland and had never had any symptoms of dysentery. The strain of limax was one which was cultivated from a perfectly typical case of amœbic dysentery during an acute stage in a patient living in Manila. The inoculation of animals with these strains was carried out by injection into the cæcum.[10 11] Although it has been shown definitely that cultures of the limax group can neither produce symptoms nor colonize in man, yet for completeness' sake two kittens were inoculated with overwhelming quantities of a culture of free-living amœbæ. The failure to produce any symptoms, or even colonize temporarily, furnishes one more example of the similarity of the behavior of amœbæ in man and lower animals; accordingly, it furnishes still further proof that the atypical amœbæ, just described, were the ætiologic factor in these cases, and that the symptoms obtained in kittens were not an artificial result of the special conditions under which the inoculations were made. For convenience, the cardinal features characteristic of these strains are presented in the following outline.

OUTLINE OF VARIOUS SPECIES AND STRAINS OF AMŒBÆ.[1]

Strain of amœbæ.	Morphology.		Parasitism.	Pathogenesis.	Virulence on passage.	Pathology.	Symptoms in man and animals.	Effect of emetine therapy.	Cultivability on agar.
	Character of nucleus.	Usual number of nuclei in cysts.							
Histolitica.	Chromatin poor.	4	+	+	Increases.	Ulcers.	Dysentery.	Good.	0
Coli.....	Chromatin poor.	8	+[2]	0[2]	....	0	0	?	0
Limax	Chromatin rich.	1	0	0	....	0	0	....	+
Atypical strains.	Intermediate.	2 & 3	+	+	Increases.	Variable	Diarrhœa.	Poor.	0

[1] In order to express these factors in tabular form, it has been necessary to select only the cardinal features, and in the case of the atypical strains the data represent the more extreme examples. In addition to these four groups of amœbæ, it is distinctly possible that other types may exist which would represent intermediate stages in the process of evolution, such as the occurrence of a group capable of leading either a saprophytic or a parasitic existence.

[2] According to Schaudinn.

From this outline it is seen that these unidentified strains differ distinctly in their morphology, pathology, and pathogenic properties from both *E. histolytica* and *E. coli*. The morphology of the vegetative stage of these atypical strains is fairly characteristic and the variation from *E. histolytica* and

FIG. 1.

FIG. 2.

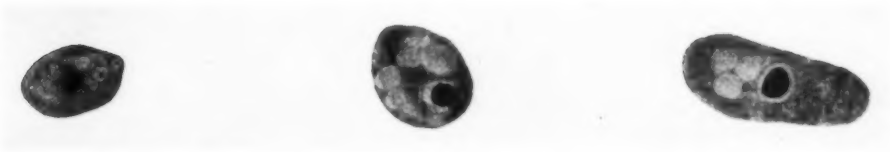

FIG. 3.

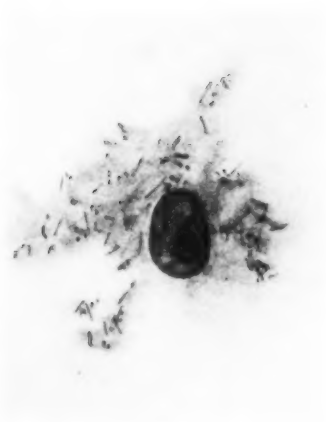

FIG. 4.

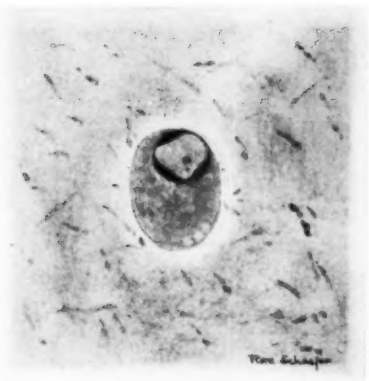

FIG. 5.

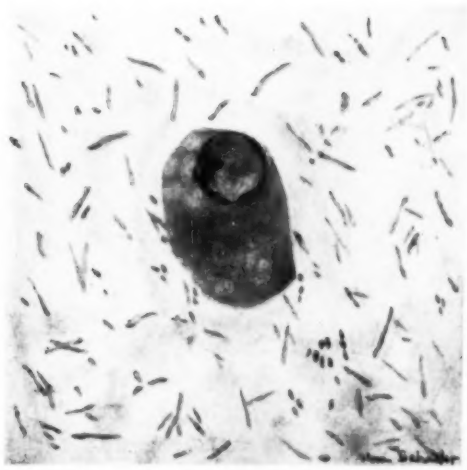

FIG. 6.

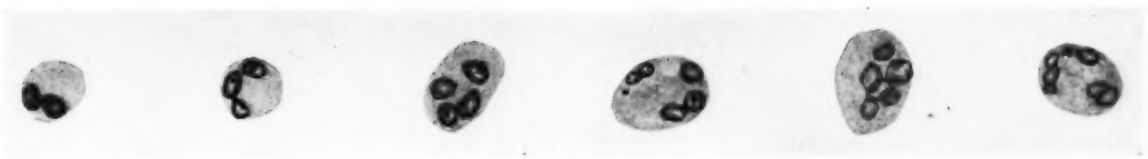

FIG. 7.

FIG. 8.

E. coli is much more marked than the differences between these two species themselves. Also in the method of forming the propagative stage, these strains of amœbæ differ from the two established types, since the predominant number of nuclei was only two and three, as compared with four and eight for histolytica and coli. In correlation with these differences in morphology, the clinical symptoms produced by these strains were at marked variance with those of typical dysentery. These differences in morphology and clinical symptoms were distinctly more marked than in other protozoan diseases in which separate species are recognized. For example, in the three types of Leishmaniasis the morphology of the parasites is so nearly identical that no constant differences are uniformly recognized by protozoologists; at least the species differentiation of *Leishmania donovani*, *L. infantum*, and *L. tropica* rests not upon differences in morphology, but upon the different effects produced by these parasites when acting in different parts of the body, their behavior upon animal inoculation and similar factors.* Nevertheless, there are two features of importance in the preceding data which militate strongly against accepting these strains as altogether distinct from histolytica, when one considers the rigidity of the qualifications necessary for the establishment of a distinct species. In the first place even the most atypical of these cases (A) gave a fairly typical history of dysentery in the early years of his disease. Moreover, these three cases represent varying gradations between an extremely obscure form of diarrhœa on the one hand and the typical histolytica dysentery on the other. This is even more striking when some other mild cases of ordinary amœbic dysentery are considered, which were observed simultaneously with these.† Likewise, the morphology does not always conform to one extreme or the other, but in a series of cases all gradations are seen between the chromatin poor and the relatively chromatin rich nucleus. Furthermore, the features which characterized these atypical strains, although constant over a long period in a given patient, changed in a few months upon subinoculation in animals. Even in the most extreme case there were signs of increasing virulence accompanied by changes in morphology toward the histolytica type after a few passages through animals.

In view of these considerations it seems advisable to conclude that the virulence and other biological characteristics of *E. histolytica* are subject to some variation and that, with changes in environment, the morphological characteristics may vary. These variations occur both in the trophozoites and in the encysted stage. Features such as the amount of chromatin and its arrangement in the nucleus are not absolutely fixed characteristics, but are subject perhaps to more variation than has been suspected. A phenomenon that is even more surprising and important is the lability in the number of nuclei in the cysts. In these strains, developing under apparently unfavorable conditions, the mature number of four nuclei is not produced, but two- and three-nucleated cysts predominate.* It was first observed by Hartmann [8] that *E. histolytica*, when infecting lower animals, undergoes, even in a short period of time, definite changes in morphology, resulting in the so-called "smal' generation," probably the *E. minuta* of Elmassian. It seem very natural, therefore, that the same phenomenon should develop in human infections. This observation by Hartmann offers further evidence in support of the view that these atypical strains of amœbæ have developed from *E. histolytica*. The clinical histories indicate that this development has taken place during the progress of the disease in a single individual; moreover, changes in the opposite direction can be brought about under experimental conditions resulting in a return from the atypical morphology toward the histolytica type. Therefore, there is not sufficient ground at present to classify these strains as a distinct variety of amœbæ, but we prefer to consider that they constitute merely a temporary alteration in histolytica which has been brought about by changes in environment.

Morphologically the trophozoites do not differ essentially from a new entamœba of man described by v. Prowazek,[13] *E. polecki*. However, the description of this amœba, like that of *E. testudinis*, a new species described by Hartmann,[14] is based upon the vegetative stage alone. The propagative stage is not described, and the trophozoites were not studied under changing conditions of environment such as would occur in tests for pathogenesis. Accordingly we do not feel that the description of *E. polecki* is sufficiently complete to enable one to recognize it with certainty, and we do not feel that there is sufficient ground as yet to establish *E. polecki* and *E. testudinis* as distinct species.

SUMMARY.

In the diagnosis of amœbic dysentery, it is ordinarily considered essential that the presence of *E. histolytica* be demonstrated in association with definite clinical symptoms. In three cases of obscure diarrhœa it was found that amœbæ were present in the intestine, which could not be identified morphologically with either *E. histolytica* or *E. coli*. Animal inoculation proved that these amœbæ were definitely pathogenic, the symptoms which characterized the disease in the patient appearing in the animals. After a careful consideration of the various factors involved in these cases, we feel that it is necessary to diagnose amœbic dysentery (intestinal amœbiasis) under conditions in which the clinical symptoms are

*** The minor differences in the morphology of the Leishmania and the difference in clinical symptoms which they produce is certainly not more marked than in the case of *B. tuberculosis*; yet the difference between the lesions produced in the lungs as compared with those of lupus vulgaris, has never been suggested as a basis for differentiating various species of the tubercle bacillus. Recent work by Patton [12] in transmitting the parasite of kala azar to lower animals makes it possible that some of the supposed differences between *L. donovani* and *L. infantum* may be less rigid than has hitherto been supposed.**

† These have been reported in brief in a previous number of the BULLETIN.

*** We realize, of course, that the rigid standards of bacteriology are not yet possible with amœbæ, and, like all work with amœbæ, these conclusions are open to the criticism that we may have been dealing with mixed infections; but the weight of evidence is against such an interpretation.**

distinctly atypical and the amœbæ present vary markedly in their morphology from *E. histolytica*. Indeed, amœbic dysentery must sometimes be diagnosed in the absence of trophozoites and when only two- and three-nucleated cysts are present. A diagnosis under such conditions should be confirmed by the inoculation of animals.

As regards the systematic position of these strains, and their relation to histolytica, definite evidence was obtained that the amount of chromatin which characterizes the nucleus of *E. histolytica* may undergo fairly marked variation. Also the number of nuclei in the propagative stage has always been considered as being sufficiently constant to furnish a satisfactory basis for the differentiation of species. In these strains marked variation occurred in the number of nuclei in the cysts, sometimes only two and three being found, and under other conditions four and often five or six nuclei. Consequently we prefer to regard the strains of amœbæ occurring in these cases, not as a new variety, but as an atypical *histolytica* temporarily modified by environment.

For the present it seems permissible to recognize only two entamœbæ of man, namely *E. histolytica* and *E. coli*. We do not feel that *E. polecki* (v. Prowazek, 1912), found sometimes in man, or *E. testudinis* (Hartmann, 1910) of certain animals can be accepted as distinct species, in view of the limited information concerning the characteristics of the vegetative stage under changing conditions of environment, the absence of specific tests for pathogenesis in a susceptible host and the absence of information concerning the propagative stage.

This paper is the last of a series of four publications on amœbic dysentery, beginning in the June number of this BULLETIN in 1914. A brief summary of these has appeared in a recent number of the *American Journal of Tropical Diseases and Preventive Medicine*. These studies have been conducted during the past year in the clinic of Professor Barker. It is a pleasure to express our appreciation to Dr. Barker for his interest in this work.

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ILLUSTRATIONS.

(Magnification × 1500.)

FIG. 1.—E. hystolitica.
FIG. 2.—E. coli.
FIG. 3.—Group of three limax amœbæ from culture.
FIG. 4.—Atypical amœba found in patient A.
FIGS. 5 and 6.—Amœbæ from first passage of atypical strain A in animals.
FIG. 7.—Series of cysts showing varying number of nuclei in atypical strain from patient A.
FIG. 8.—Pus cell simulating an amœbic cyst.

EXPERIENCES WITH THE PHENOLSULPHONEPHTHALEIN METHOD OF TESTING THE FUNCTION OF THE KIDNEY.[1]

BY OTTO HESS, M. D.

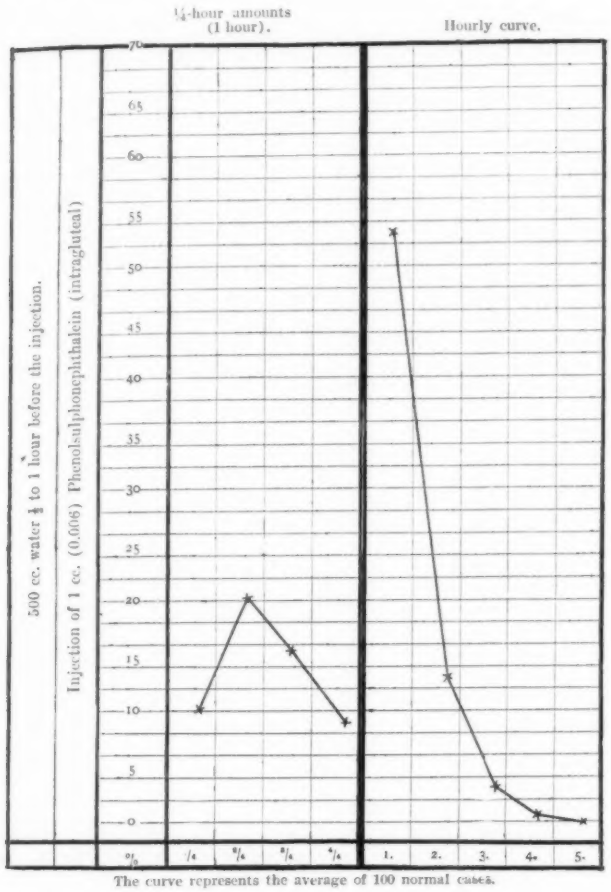
(From the Medical Clinic of the Cologne Academy for Practical Medicine. Director: Prof. Dr. Moritz.)

It is not my intention to give a lecture on the well-known methods of testing the function of the kidney, but merely a report of the results of 300 tests made by the Rowntree-Geraghty methods.

As has been previously noted by Rowntree and Geraghty, phthalein was found in the urine of healthy persons five to ten minutes after injection. After noting the time of the first appearance of the phthalein in the urine, hourly determinations were made by these authors. Under normal conditions the first positive reaction occurs almost constantly five minutes after injection, while in renal diseases the time of the first appearance of the phthalein may be delayed one hour or more. For this reason, observations were begun at the time of injection. Assuming that there is a difference in the excretion of the healthy and diseased kidney during the first hour, and in order to note the time of the first appearance of the phthalein, the urine was collected every 15 minutes during the first hour after injection. At the same time I hoped, by stating the normal curve for the first hour, to reduce the observation time of four hours, and thereby make the method more adaptable for the use of the private practitioner; but it is of considerable advantage to know the total excretion. There exists for the healthy kidney a typical curve of excretion for the first four 15-minute periods. Under normal conditions the quantity excreted during the first 15 minutes is a measurable amount, which increases during the second 15 minutes, rarely increases during the third, decreases during the fourth, and then steadily drops to zero. This has been noted in many observations made at regular 15-minute intervals. In making hourly estimations, the curve shows a large amount at first, a rapid

[1] An address delivered before the Rhine-Westphalian Society at Bonn, May 12, 1914.

decrease in the second hour, and then a gradual decline until the test becomes negative.[2]



The curve represents the average of 100 normal cases.

PHENOLSULPHONEPHTHALEIN CHART.

Before discussing the results of the test in disease, it is well to note that even normal kidneys may show certain variations in excretion. As previously noted,[3] I have frequently obtained in the same patient a more rapid and complete phthalein excretion in the afternoon than in the forenoon. This may be attributed to stimulation caused by the ingestion of food, since phthalein itself does not stimulate the action of the kidneys. It is important to remember that these variations are not observed in renal diseases.[4] Furthermore, decreased amounts of phthalein are excreted by apparently healthy kidneys, which may be due to a decreased urinary output or some pathological changes in the urogenital system. Occasionally cases are noted which, though quite normal, show a variation in the amount of phthalein excreted without any diminution in the amount of urine. These are, however, rare exceptions.

Regarding the reliability of the test in diseases of the kidney, I have found, in every case of kidney disease confirmed by autopsy or operation, an abnormal phthalein excretion closely parallel to the severity of the condition. The most striking results were obtained in the various forms of chronic nephritis. The time of the first appearance of the phthalein is delayed and the amount excreted diminished, or the curve is abnormal. In most cases the duration of the excretion is prolonged. The more severe the disease, the greater is the deviation from normal. Dietsch and others state definitely that there is a parallelism. Rowntree and Geraghty describe several cases in which they were able to predict an uræmia solely from the abnormal phthalein excretion. My own observations allow me to say that all cases showing an abnormally low or an entirely absent excretion allow of a very bad prognosis. Repeated tests during the course of treatment enable one to decide whether the treatment is beneficial or whether the nephritis is incapable of any improvement.

One great advantage of this method is the possibility of diagnosing nephritis without any previous dietary preparation in many cases which are clinically doubtful. These are the patients who complain of slight cardiac distress and frequent headache. They generally have a high blood-pressure and a slight cardiac enlargement, but the urine presents nothing abnormal. We know that these patients suffer from chronic nephritis, but the phthalein test is the only one to quickly confirm this fact. Daily examinations of the urine occasionally show slight traces of albumin and sometimes a few casts.

In acute diseases of the kidney, in toxic derangements thereof and amyloid kidney, the results of the phenolsulphonephthalein test are not so clear, and occasionally quite contradictory. Cases of acute renal disease often show a relatively good excretion of phthalein despite severe clinical symptoms (albumin, cellular elements in abundance, and œdema). As these patients improve, the excretion of the phthalein rapidly becomes normal. On the other hand, there are patients with clinically these same symptoms and a comparatively good phthalein excretion, but as they clinically improve, the phthalein excretion gradually grows more abnormal, and the excretion of NaCl and the diastase content decrease at the same time and in the same degree. There we see an acute disease of the kidney gradually grow to be one of a chronic type with permanent tissue changes.

In other forms of kidney disease the excretion varies with the severity of the condition. In uncomplicated amyloid disease the excretion appears to be practically normal, but there are a few cases where the excretion of phthalein does not quite parallel the renal changes. These require further investigation.

In applying the Rowntree-Geraghty test it is always necessary to take into consideration extra-renal influences, especially those from the heart. In cases of cardiac insufficiency the phthalein excretion is delayed, which may be attributed to

[2] At the suggestion of Professor Moritz a chart was arranged to show the normal average curve of phthalein excretion in 100 cases. This chart, of which the one that appears here is a modification, also contains space for notes regarding the condition of the heart and kidneys. The full chart, with a detailed description of the method, can be obtained from F. Hellige & Co., Freiburg, in Breisgau.

[3] Hess: Muench. med. Wchnschr., 1914, Nr. 51.

[4] Further researches on the effects of the phthalein test are not included.

delayed absorption of the phthalein. In cases where cardiac weakness is responsible for the kidney affection, the excretion of phthalein increases and becomes normal as the cardiac condition improves. In croupous pneumonia we often find that the excretion of phthalein is subnormal, being parallel with the NaCl retention. As soon as the crisis is over, it returns to normal unless there is some chronic renal disease in addition to the pneumonia.

The phthalein excretion is abnormal in all cases where sodium chloride and urea or one of them is not excreted in a normal amount. Investigations recently made in our clinic by Herr Caan,[5] have also shown that in almost all cases there is a parallelism between the diastase content of the urine and the phthalein excretion. In chronic nephritis, the importance of this observation is very striking.

From these facts a most important conclusion, especially for general practice, may be deduced. It may be assumed that whenever the excretion of phthalein is abnormal, the excretion of NaCl and of nitrogen by the kidneys is also deficient, and that this simple test might take the place of the more difficult sodium chloride test, although for clinical purposes the NaCl and other tests are of great importance. It must be remembered that the addition of 10 gm. of NaCl to the diet of a patient suffering from nephritis may produce unfavorable symptoms almost uræmic in character. Consenz[6] also considers this a dangerous procedure.

In conclusion, let us consider briefly the phenolsulphonephthalein test in renal diseases other than nephritis. My cases of unilateral renal disease, nephrolithiasis, pyonephrosis, etc., some of them confirmed by operation, show that the phthalein test is valuable for determining the amount of work each kidney is capable of doing. It is superior to other color tests in the accuracy of the information it yields. The result of the phthalein test shows how much of the parenchyma is involved, and is of much value in the differential diagnosis of doubtful renal tumors. The Rowntree-Geraghty test is regarded with favor by most observers, but in some published cases where subnormal amounts were excreted from apparently healthy kidneys, previous mention is made of the existence of tumors, pregnancy, etc. Ware has recently published a paper, of which I have only been able to obtain an abstract, in which he claims that the phthalein test is worthless. My investigations do not confirm his opinion. Although there may be some cases with severe clinical symptoms in which the test unexpectedly shows good renal function, we are nevertheless justified in concluding that the phthalein test surpasses all other similar methods by its simplicity. It can be applied immediately without any dietary preparation, and can be used in all cases, even uræmic conditions. The result is rapidly obtained, and is of value both for diagnosis and prognosis. The parallelism between the excretion of phthalein, NaCl and nitrogen is of great importance, and diet and treatment may be prescribed from the results of the Rowntree-Geraghty test alone in cases which could not be recognized as chronic nephritis by the clinical methods hitherto available. A more extensive article on this subject will be published in the Muenchener medizinischer Wochenschrift.

[5] Will appear shortly in Deutsh. Arch. f. klin. Med.

[6] Consenz: Arch. f. klin. Med., Bd. 108, S. 353.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

DECEMBER 7, 1914.

An Operation for Hypophyseal Tumors. Exhibition of Case.*

DR. G. J. HEUER.

Dr. Heuer described an operation for attacking lesions of the hypophysis, and presented a patient upon whom this operation had been done. He discussed the various methods of approaching hypophyseal lesions and noted their disadvantages and their impracticability in permitting a thorough operation. These operations include the transphenoidal operation as employed by Hirsch, Cushing and others and the intracranial operations of Krause, McArthur, Fraser and Killiani. The advantages of the operation as proposed are a very much more extensive view of the entire chiasmal region, and even, to a certain extent, of the region behind the chiasm. Both carotid arteries are easily exposed and the entire field is under control. The operation as described consists of a large, low, frontal osteoplastic flap. Following this, the dura is opened almost as widely as the bone defect. Lumbar puncture is then done, the head tilted backward and, by gravity, the frontal lobe falls away. Further exposure is obtained by retraction with the spatula, which is introduced laterally, *i. e.*, just in front of the temporal lobe. In two cases this method was employed and in each instance the results were most satisfactory.

* To be published in full later.

The first case was presented at the meeting. The patient was a boy, aged 10, who had had complete blindness in one eye, hemianopsia in the other and a gradually increasing headache. There was also involvement of the third and fourth nerves, as indicated by complete ptosis on the right side and a wide inert pupil with absence of all reaction. The X-ray showed a greatly enlarged sella turcica. The discs showed pallor, indicating optic atrophy. There were no glandular symptoms referable to the hypophysis. At operation a large, bluish cyst protruded above and between the optic nerves. This was opened and a large amount of blood-stained fluid evacuated. The patient's recovery was very satisfactory, as vision returned almost entirely. All the palsies disappeared and he remained well for about six months, when the symptoms gradually returned. He is now in practically the identical condition in which he was on the first admission. In addition, he has grown fat.

The second patient was a girl, aged 19, with blindness in one eye and almost complete loss of vision in the other. There was some adiposity, increased sugar tolerance, intermittent polyuria and sexual disturbances. The sella turcica appeared normal in the X-ray. It was evident that the tumor was of supra-sellar origin and could not be attacked by the transphenoidal route. At the operation, as described above, a cyst was found behind the optic chiasm, probably arising in the infundibulum, although its exact origin could not be determined.

Complement Fixation in Thyroid Diseases.* DR. S. R. MILLER.

The tendency in recent times to devise functional tests for the various glandular organs of the body, has now come to embrace the so-called ductless glands, about which there is so much of interest at present. The frequency of thyroid conditions, and especially of states of hyperthyroidism, makes it desirable that functional tests for the activity of the thyroid gland be available, especially for the diagnosis of border line cases. This need was called attention to by Dr. Barker in 1914; he mentioned that there were at that time four tests of this nature, namely, Reid Hunt's acetonitrile test, tests for hyperadrenalinemia, Abderhalden's dialysis test, and finally the complement deviation test of Roseo. For numerous reasons, it was decided to try out the last-named test. For the purpose of antigens various extracts were prepared from thyroid tissue removed at operation in cases of Graves' disease. After submitting the various extracts to suitable titrations the sera of a number of patients suffering from Graves' disease, other thyroid conditions, unexplained tachycardias, dementia præcox, and known cases of lues, were submitted to complement deviation tests, according to the well-known method of the Wassermann reaction. The results in a series of cases were remarkably negative, even when each serum was tested against a total of 19 or 21 different antigens. No positive findings in any thyroid conditions were observed. The only sera which gave complement fixation were those from cases of known lues, which showed a positive Wassermann reaction as tested in the usual manner. Similar positive results were secured when spinal fluids from cases of general paresis were employed. It would seem, therefore, that the test of Roseo is of no clinical value in the diagnosis of thyroid conditions.

The Results of the X-Ray Treatment of the Thymus Gland in Graves' Disease. (Abstract.) DR. W. S. HALSTED.

In an address before the New York Academy of Medicine last year (March 14, 1914), I called the attention of American physicians to the fact that the thymus gland may play an important rôle in Graves' disease.†

My remarks tonight are intended as a continuation of the address referred to, which was published last August in THE JOHNS HOPKINS HOSPITAL BULLETIN. It may be assumed that very few of our audience this evening read the midsummer numbers of medical journals, and hence, in order to make intelligible the special facts which I desire to emphasize at this time I shall make an occasional draft upon my previous paper.

Less than four and one half years ago Meltzer ‡ made the following cautious statement concerning the thymus gland: "With our present knowledge of the importance of the other ductless glands we are hardly justified in assuming that the thymus is a worthless fetal remnant. But we have to acknowledge that as yet there are no reliable observations or experiments which indicate clearly that the thymus has a function in postuterine life."

My interest in the thymus was greatly stimulated by the report of Garré in 1911, at the Fortieth Congress of the Deutsche Gesellschaft für Chirurgie, of a case in which he had primarily removed the thymus for the cure of Graves' disease. Although well aware of the fact that a persistent or revivified thymus had repeatedly been observed in Basedow he was astonished to learn from the statistics obtained by his assistant, Dr. Capelle, that a thymus persistens hyperplastica had been found in 95 per cent of the fatal cases, whether death was due simply to the severity of the disease, or occurred during the operation, or within 24 hours after the strumectomy.

Selecting a florid example of Graves' disease for his experiment he exsected the thymus without molesting the thyroid. The result in this, his first case, was as follows: "Clinically no definite influence on the struma, the exophthalmos or the eye symptoms, but an unequivocal improvement in the general condition as expressed by the signal quieting of the heart's action, rapid increase in weight, and a complete regression of the Kocher blood-picture, the lymphocytes falling from 40 to 25 and then to 10 per cent." Prof. Garré gave to his assistant, Dr. Capelle, credit for the work and for the thought which led them both to these conclusions, which, he said, find essential support in the proof by Klose that in the thymus substance there is a heart poison. Aside from the special action of the thymus there exist certainly, said Garré, important reciprocal relations between these two glands. Reasons for this view are given in my Harvey Lecture.

In the three and a half years which have elapsed since Prof. Garré's report, research work on the thymus, which already had been considerable, has assumed large proportions, and the interest of surgeons and also of physicians, particularly in Germany, Russia, Switzerland and Italy, in the possible part that the thymus may play in Graves' disease has been thoroughly aroused. I am hoping each day that there may appear from our country a contribution to the subject. Up to the present time I have seen no reference made to it in the American or English literature. Operative confirmation of the correctness of the view of Garré and Capelle and, I should add, of Hart and Rehn and Klose and Sauerbruck and others is given in two papers by von Haberer.* Most convincing is the report of case 3 in von Haberer's first paper.†

For a fuller consideration of the operative side of the question, I must again refer you to my paper.

To-night we are concerned simply with the results of the X-ray treatment of the thymus in Graves' disease. Rudberg, Aubertin and Bordet, Pigache and Béclère, Arella, Heincke, Peters, Klose and others have shown that under the influence of the X-ray the thymus rapidly undergoes involution, an involution which is so extensive that Klose expressly warns against radiation of the thymus region in children. Heeding this warning I excised portions of the thymus in two cases of Graves' disease in children, fearing to submit them to the risk of the X-ray treatment. In my paper (pp. 231 and 232), to which for the sake of brevity I have had occasion to refer so frequently, a brief reference is made to the result which followed treatment by radium ‡ of a patient upon whom in two stages a double thyroid lobectomy had been performed about two years previously. The effect of this treatment was so astonishing that I promptly wrote and telegraphed to six selected patients, those in whom the improvement after double thyroid lobectomy had been particularly unsatisfactory, urging them to return to the hospital as soon as possible. All of these patients responded promptly to my call, one coming from as far as Texas, making a journey which required four days. I wish here to express my gratitude to these patients, and my indebtedness to Dr. Baetjer and to Dr. Waters who have given the X-ray treatments to these six cases of double lobectomy and indeed to all of my new and to many of my old patients with Graves' disease.

As nearly a year has passed since this treatment was first tested I feel that we may now with considerable assurance speak of the results.

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* This article is to be published in full in a later number of THE JOHNS HOPKINS BULLETIN.

† Harvey Lecture. The Significance of the Thymus Gland in Graves' Disease. March 14, 1914.

‡ Meltzer: Animal Experimentation in Relation to Our Knowledge of Secretions, Especially Internal Secretions. Proc. of the Path. Soc. of Phila., 1910.

* von Haberer: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1913, Bd. 27, S. 199. Arch. f. klin. Chir., 1914, Bd. 105, S. 296.

† An abstract of this case as it appears in the August number of the BULLETIN was read by Dr. Halsted.

‡ The radium treatment was very kindly given to this patient by Dr. Burnam in the sanatorium of Dr. Kelly.

In the six cases in which after double lobectomy the result was unsatisfactory the X-ray treatment was begun in March, April or May, 1914. The time elapsed between the surgical operations and the treatment by radiation was 4½ years (one case), 3 years (one case), 2 years (one case), 1 year (one case), 10 months (one case), 6 months (one case).

Four of these cases were so ill on admission that ligation of the thyroid arteries was done in two or more stages preliminary to the first lobectomy. In two cases the four arteries were tied before excision was ventured. All of the patients were greatly improved by the operations and from being bedridden and in a pitiful state were enabled to go about moderately and find some pleasure in existence. But in none was the result satisfactory to myself, although four of the six cases were more than content with the relief which they had obtained from the operations. In only one case was there perfectly definite retrosternal dulness and X-ray shadow.

In each case the result of the radiation was prompt and striking. The improvement was so great that without exception the patients expressed delight at the result. Two state that they are "perfectly well." Two young women, and the youngest of the six, who were greatly discouraged by the inadequate operative relief, have now, with occasional exceptions, a normal pulse and enjoy life almost to the full; one, however, is still concerned about the incomplete subsidence of the exophthalmos which was extreme, and the other is easily fatigued. Each of the cases presents features of special interest which I hope to record at some other time. For example, in one pigmentation and in two the yellow pasty hue of the skin disappeared after the X-ray treatment.

In two, pronounced eye signs were improved almost immediately.

In three, headache, which had been more or less constant, was the first symptom to vanish and has not returned.

Asthenia, which was common to all the cases, has been particularly influenced.

In one, pronounced agoraphobia has seemingly been cured. This patient who formerly dreaded crossing a street now threads crowded thoroughfares without concern.

It is interesting to note that in no instance did the lobectomies fail ultimately to restore the blood-picture, to reduce the percentage of lymphocytes when this had been too high. This was hardly to have been expected in cases so definitely relieved by radiation of the thymus as to indicate persisting overactivity of this gland.

I quite agree with Prof. Kocher and Dr. Albert Kocher that strumectomy in Graves' disease restores after a time the normal blood-picture and that, therefore, in case the thymus is responsible for the high lymphocytosis, excision of the thyroid must correct in this respect the overactivity of the former gland.

But the fact that after double lobectomy without adequate relief, radiation of the thymus was followed by great improvement would indicate that the thymus was still uncontrolled, and this being the case, suggest that the high lymphocytosis may not have been caused solely by the thymus.

Is it conceivable that the persistent cells of the complex thymus, those causing the symptoms which were relieved by Roentgenization, may not be the ones which gave rise or give rise to the lymphocytosis; or that with the degeneration and waning power of the cells their ability to sustain the lymphocytosis may be lost while they may still be responsible for the unrelieved symptoms? On the other hand, can we be sure that there is not sufficient diffusion of the rays aimed at the thymus to affect the remains of the thyroid lobes? This suggestion is scouted by the radiologists.

I have in mind a case of double lobectomy in which a tiny fragment of the isthmus of the thyroid became greatly hypertrophied after the operations, and disappeared entirely 48 hours after treatment of the thymus by radium.

Of very especial interest to me are the conclusions given by Dr. Albert Kocher of Bern in an admirable paper, Ueber Basedow'sche Krankheit und Thymus, which he presented at the meeting in Berlin last April of the Deutsche Gesellschaft für Chirurgie. Dr. Kocher's views have, undoubtedly, the endorsement of his father, Prof. Theodor Kocher.

They are as follows:

"Basedow's disease without hyperplasia of the thyroid gland has not as yet been proved at autopsy or by operation.

On the other hand, a considerable number of typical Basedow cases, with all the characteristic symptoms, have been observed in which no histopathological alteration of the thymus was found.

It is, however, remarkable that in quite a large number of the Basedow patients there is found a late hyperplasia or late involution of the thymus. We estimate the number of these, on the basis of clinical and anatomical findings, at 45 to 50 per cent of all Basedow cases.

The thymus-hyperplasia is much more common in the young than in the old Basedow patients. The age of most frequent occurrence of thymus-hyperplasia does not correspond with that of the commonest age for Basedow.

From the weight alone of the thymus no conclusion can be drawn as to the amount of thymus-parenchyma which may be present.

In the great majority of cases of Basedow with combined thymus-hyperplasia there is only a moderate enlargement of the thymus (15 to 30 grams). It is rare to find in them a gland weighing 50 grams. Equally heavy thymus glands occur without Basedow.

The histological examination of our Basedow-thymus glands by Pettavel as well as those of von Haberer has shown that, without exception, there has been a mixed hyperplasia of cortex and medulla, and that histologically no difference existed between the hyperplasia of childhood and that of Basedow.

In 21.5 per cent of the Basedow-thymus glands there are definite signs of an age-involution with abnormal amount of parenchyma; in 14.2 per cent distinct indications of pathological involution with excessive parenchyma-mass.

Thymus-hyperplasia is much more common in some regions than in others, also in certain families, in which it occurs with and without Basedow. The examinations which have hitherto been made, especially the anatomical, make it probable that we are dealing with a regionary family persistence, or late hyperplasia and late involution established upon a congenital or, if you will, constitutional base.

Clinical observations suggest that, at least in certain instances, there supervenes with the Basedow a further hyperplasia or revival, a regeneration in other words, of thymus-parenchyma, which, with the cure of the Basedow, for the most part disappears. That there is such a revivification or regeneration we can only surmise, for we have up to the present time no anatomical proof of it in man.

Accordingly, hyperplasia of the thymus would be present, for the most part, before the Basedow and could not, therefore, be the direct cause of the disease, especially as we find the same hyperplasia present in individuals who have at no time in their lives suffered from Basedow.

The cause of the thymus-hyperplasia might stand in direct relation to the hypoplasia of the medulla of the adrenals.

In accordance with biological laws it is certainly rather to be assumed that an organ is congenitally hypoplastic and in consequence another hypertrophies, than that congenital hyperplasia of one organ is responsible for hypoplasia of another.

Hypoplasia of the adrenal-medulla in Basedow's disease was first demonstrated on our material by Pettavel; it is found with and without thymus-hyperplasia. In Basedow there occurs a cellular hypertrophy in the hypoplastic suprarenal-medulla.

Both of the changes, adrenal-hypoplasia and thymus-hyperplasia, remain latent in most cases until the onset of the Basedow, wherein, by the altered function of the thyroid, there is called forth a disturbance in compensation.

Up to the present moment it cannot definitely be said whether

we may attribute certain of the symptoms of Basedow's disease to changes in the adrenals and the thymus, or whether we may do so only in certain cases.

As proof that the adrenal-hypoplasia was present in latent form before the manifestation of Basedow we regard the appearance and disappearance of certain symptoms synchronously with the vanishing of the Basedow, symptoms which one observes in cases of atrophy of the adrenals without Basedow; we mention only the melanodermia of certain Basedow patients.

Something similar may exist for the thymus-hyperplasia. We have, therefore, emphasized the above symptoms as occurring in Basedow with thymus.

To this extent can one speak of a special action of the thymus and adrenals and of special symptoms attributable to the influence of these organs in Basedow's disease.

For the view that a typical Basedow picture, without thyroid hyperplasia, can be evoked by the hyperplastic thymus we have up to the present moment no support.

For the therapy of the cases of Basedow complicated with thymus-hyperplasia, the following conclusions present themselves:

In these cases, also, the disease is recovered from by sufficient reduction of the hyperplastic thyroid, provided operation is not too long deferred. The thymus-hyperplasia then gradually regresses.

The thyroid operation is in these cases not more dangerous than in the Basedow patients without thymus.

Basedow with a high degree of thymus-hyperplasia, as is more frequently observed in younger individuals, is cured only by earliest possible operation upon the thyroid gland.

In these cases, as also in those in which obdurate symptoms persist, and further when there is a tendency to recurrence, thymectomy may with advantage be added to the thyroid excision.

The indication for thymectomy in Basedow's disease may be determined not only by the existence and severity of certain symptoms but also by the result of the test-administration of preparations of the thymus and thyroid glands. A preliminary treatment, before the thyroid operation, with thymus preparations and with Roentgen-radiation of the thymus is indicated in cases which react favorably to these procedures. Such treatment is, however, only temporary in its effect; especially is this true of the radiation, and it must therefore be undertaken only a short time prior to the operation upon the thyroid gland."

Dr. Kocher's opinion that the effect of the X-ray in cases of Graves' disease is transient might seem, at first thought, not to accord with our experience. But our views do not necessarily conflict. In Professor Kocher's clinic the Roentgenization of the thymus was done before the strumectomy, whereas in our six cases of double lobectomy it was after the final operation upon the thyroid—in one case 4½ years thereafter. We believe with Dr. Kocher that there is probably a regression of the hyperplasia of the thymus after strumectomy. Granting this, it is presumable that the Roentgenization of a gland (the thymus) at a time when there is a continuous tendency to degenerate should be more effective and more permanent in its results than in the period of its greatest activity, particularly when this hyperactivity is being constantly sustained by the stimulation of another organ (the thyroid gland).

Roentgen Technique in the Treatment of the Thymus Gland in Graves' Disease. DR. C. A. WATERS.

The technique employed in the treatment of Graves' disease by Roentgenization of the thymus gland has been uniform throughout and the observations have been made from sixty cases. Different types of cases and different stages of the disease have been dealt with, as related by Dr. Halsted.

The treatments were divided into three series, with intervals varying from two to three weeks between irradiations. Six treatments were given in each series, over the anterior chest wall starting in the first interspace on the right side close to the sternal margin, through a portal of entry 5 cm. in diameter. Irradiations were given in the majority of cases on six successive days in the first, second and third intercostal interspaces along the right and left sternal margin; however, a number of the patients received six treatments at one seance. The patients were then allowed to wait until two weeks had elapsed after the last treatment before beginning the second series of irradiations.

They were again treated in the same manner as before, and a like interval of time allowed, before receiving the third or final series; therefore, no cases have received more than three series, or eighteen treatments, and some only one and two series comprising six and twelve treatments respectively. Each individual irradiation consisted of a six-minute exposure, given through a 1 mm. aluminum filter at a focal and pastille distance of 20 cm. We have used the full pastille distance, that is, the same as the focal distance; and contrary to the general rule of inverse proportions of multiplying by the square of the inverse of one-half the distance, which would be four, we have multiplied the skin dose (3 H) by 2½ ; thus we have given a dose of 7½ H units through each portal of entry, at each sitting; this constituting the erythema dose. So each area received the erythema dose, 7½ H, three times or 22½ H, the six areas receiving a total dose of 135 H.

The Holzknecht, Sabourand-Noire and Benoist radiometric systems were employed throughout the work, and the unexposed parts of the body were covered with a 1 mm. lead sheet, the chest wall being reinforced by a 3 mm. lead protector.

A parallel spark-gap of seven inches, tungsten target and coolidge tubes with 5-7 milliamperes of current were used.

In the sixty cases treated only one atypical reaction occurred, a brilliant blush coming on thirty minutes after receiving the last dose of the third series and lasting as such for six weeks, gradually fading away with no vesiculation or other ill effects.

The normal skin reaction after Roentgenization in the manner described consists of a definite faint blush, which appears in from one-half hour to six hours after irradiation, usually lasting from one to two weeks, gradually fading away followed by slight pigmentation, which by the end of three weeks has also entirely disappeared.

Some Medical Aspects of Hyperthyroidism. (Abstract.) DR. L. F. BARKER.

Though papers of importance upon pathological conditions of the thyroid have appeared, there has been but little new published during the past year bearing upon the functions of the normal thyroid. One of the most interesting reviews of the newer work recently published is that of F. Kraus, who presented the subject at the International Congress in London (1913). He emphasized an idea which has been growing among clinicians, namely, that the hormonic substances produced by the thyroid gland influence electively the continuous-tonic innervations in the domain of the vegetative nervous system, and also the autochthonous vital processes of the tissues themselves. That is to say, it is believed that the thyroid hormones may influence directly the actual cell life, independently of, as well as through the intermediation of, innervations. It is even possible that the particular influence of the thyroid on metabolism may concern the autochthonous processes of the tissue cells directly.

The idea that Graves' disease is not merely a hyperthyreosis but is also a dysthyreosis seems to gain support. In other words, the condition is not due simply to an overactivity of a hypertrophic normal gland, but is the result of an actual perversion of secretion in a pathologically altered gland.

Dr. Halsted has spoken of the reciprocal relations of the thyroid and the thymus. Certainly, the newer studies indicate that a large number of patients suffering from Graves' disease are also "thymus carriers"—at least 50 per cent of the severer cases. In nearly

all of the fatal cases examined, an enlarged thymus has been found at autopsy.

Several papers have dealt with the vagotonic and sympathicotonic phenomena in Graves' disease (Eppinger and Hess, C. von Noorden, Jr., Barker and Sladen, and others). In our experience here, and this I think is the general experience elsewhere, most of the cases are "mixed," there being nearly always symptoms that are "vagotonic" along with symptoms that are "sympathicotonic" in the same patient. This appears to be true, especially of the patients with marked nervous and mental disturbances. The symptoms, it is true, are in some patients predominantly vagotonic in type, while in others they are predominantly sympathicotonic. In the interesting paper of Capelle and Bayer, to which Dr. Halsted has referred, an attempt has been made to establish a histological basis for both the sympathicotonic and the vagotonic influences, not only in the thyroid gland, but in the thymus as well.

The clinical difficulty of telling whether the thymus is actually enlarged or not is sometimes a very real one. If there be dulness on percussion to the left of the manubrium, or if Boggs' sign be positive, enlargement is probable. Roentgenograms are helpful in deciding whether or not the thymus is enlarged, as is also the so-called Kocher blood-picture (relative lymphocytosis).

Despite the prevalent opinion that thymotoxic influences are added to thyreotoxic injury in Graves' disease, there are still two camps among clinicians, one urging that the symptoms are due to too much thymus-activity, and the other asserting that they are due to thymus-deficiency. Thus we find reports of wonderful cures produced by feeding thymus extract on the one hand (R. Hirsch), though, on the other, good results have followed surgical extirpation of the thymus (v. Haberer, Klose), and exposures of the gland to X-ray influences.

The enlarged thymus of children with status thymicus is now frequently treated by X-rays (Sidney Lange), and the X-ray treatment of the thymus in Basedow's disease has, as Dr. Halsted has pointed out, begun to appeal to clinical men. In December, 1913, E. Stoerk made a report to the Society for Internal Medicine and Pediatrics in Vienna. In a report by Sinozersky (July, 1914) on 20 patients suffering from Basedow's disease treated with Roentgen-rays over the thymus, giving a course of four to six treatments at intervals of three or four days, a second series of exposures being entered upon at the end of three weeks, the author states that the results were so striking that he feels that the rôle of the thymus gland in the pathogenesis of exophthalmic goiter is now established beyond question. He states that under X-ray exposures, directed against the thymus, the pulse fell from 120 or 140 to 80, the other cardinal symptoms of the disease abated, and the differential formula of the white blood corpuscles became more nearly normal.

An interesting statistical article on the course of Basedow's disease has been published by Dr. Plummer of the Mayo Clinic. In the experience of that clinic, Graves' disease usually begins acutely, and reaches its acme in the second half year. The disease continues, with intermissions and exacerbations, for about four years, but not much longer. Ordinarily, cerebral irritation, vasomotor disturbances of the skin, tremor, nervous irritability, tachycardia, asthenia, myocardial insufficiency, exophthalmos, diarrhœa, vomiting, psychic depression, and icterus occur in serial sequence. The toxic phenomena and non-hyperplastic goiter tend to set in on the average about fourteen years after the development of the struma and involve predominantly either the circulatory system or the structures, abnormalities of which give rise to a picture similar to Graves' disease. Plummer postulates three toxic elements of the thyroid secretion. One injures especially the nervous system, another the circulatory apparatus, and a third causes the exophthalmos. In outspoken exophthalmic goiter, it is the element which injures the nervous system which is produced in largest amount. Very careful studies of the pathology of the thyroid gland in exophthalmic goiter were published last year from the same clinic by Dr. L. B. Wilson, and Drs. Blackford and Sandford believe that they have demonstrated the presence of a depressor substance in the serum of the blood of patients affected with this disease. The intensity of the depressor effect was proportional to the acuteness of the intoxication. In their opinion this depressor substance is neither cholin nor any ordinary peptone.

On the other hand, Kraus asserts that Retzlaff has proven that the adrenalin content of the blood is increased in exophthalmic goiter. Gley and others, like Blackford and Sandford, state that they have demonstrated conclusively that blood serum and extracts of the gland have a depressing effect, and that the blood must contain hypotensin.

As to the treatment of exophthalmic goiter, most surgeons advise operation whenever the diagnosis is definite. The majority of medical men advocate, first, conservative treatment—rest, hydrotherapy, thorough upbuilding, arsenic to slow metabolism, etc., until it is possible to see whether the patient will respond and make surgical intervention unnecessary. Some surgeons also adopt this view. Surgeons see chiefly the classic examples—outspoken cases of Basedow's disease; medical men see every transition from normal function to the outspoken Basedowian syndrome, and I think are likely to make the diagnosis of Graves' disease at an earlier stage than was formerly possible. It is surprising how rapidly some patients improve under medical treatment. Indeed, after two or three days of suitable measures there is sometimes a remarkable amelioration of the symptoms. In many instances, however, improvement is so slight that we do well to advise prompt surgical treatment.

I, too, have been interested recently in watching the effects of Roentgen-ray treatment of the thymus in some of the cases here. Some have improved markedly. Others have not, as far as I can see, improved; some have told me they were worse after the treatment. I believe that we have to deal here with another instance of a common experience in the treatment of Basedow's disease, namely, that a therapeutic measure valuable in some cases, is not helpful in all. We have not found any one thing yet that is wholly satisfactory in the treatment of all cases of Basedow's disease, but we must not fail to be grateful if in the X-ray applied over the thymus we have an agent which will help us in some cases not benefited by the remedies hitherto used.

DISCUSSION.

Dr. Janeway: I confess it seems to me that on this question of what one shall infer from the beneficial results of any therapeutic measure in relation to exophthalmic goiter, the wisest words ever said were those of Epictetus in his First Discourse: "The beginning of philosophy is the observation how men contradict each other, the search whence cometh this contradiction and the censure and mistrust of bare opinion."

Beyond that statement I do not think we are any of us in a position to go at the present moment in regard to the treatment of this disease.

I agree with Dr. Barker as to the frequency of improvement and permanent cures outside of hospital patients in the wards, even in cases of outspoken exophthalmic goiter. I could mention offhand six cases of severe type perfectly well many years afterwards; one of them a case in my own family, well after thirty years, two others of exophthalmic goiter in men and another a woman who is still living years later, and entirely free from any evidence of exophthalmic goiter, though she developed severe myocardial insufficiency, with œdema, during the disease. I have seen other similar cases in my own experience and have also seen in the last few years a great many unsuccessful thyroidectomies. There is no question in my mind at the present moment that just as in the decision between the medical and surgical treatment of gastric ulcer, the problem is very largely a social and economic one. The measures which are necessary for recovery from exophthalmic goiter under medical

rest treatment, are measures which are practically inapplicable to the bulk of patients in a hospital. My father always said that a hospital was the worst place to get results in a patient with exophthalmic goiter. Consequently, for ward patients, one resorts to surgery early. There is no question that without surgery we should be quite hopeless about many of these hospital patients, and yet I cannot feel that the surgery of exophthalmic goiter has solved the problem of the actual pathogenesis of the disease. The fact that von Haberer was able to take out tissue without a trace of thymus in it, fails to convince me that the thymus of that man had anything to do with the improvement. You may remember Dr. John Rogers' enthusiasm over the first results with his serum. He tried it on his own wife, who had one of the worst cases I had ever seen. To his discovery of the serum, she apparently owed her immediate and wonderful restoration to health. The second case did well, the third case not so well. We have seen a number of cases under serum treatment since then, but very few in whom the results have been more than partially satisfactory and failure has been the rule. The majority of us have rather given up any attempt to accomplish results with the serum, although I have seen an occasional case since where, apparently, benefit has come from its use.

We stand to-day face to face with an unsolved problem. The worst of it is there are so many opinions unsupported by adequate evidence, and so much published by people whose actual facts you have to question. We are exceedingly fortunate here in having a chance to watch cases treated by the best surgical methods and followed over a long period of time, as Dr. Halsted does, which is the only possible way we shall ever arrive at a just appraisement of the results. In the course of a few more years we ought to know whether radiation of the thymus gland is going to be valuable or not. At the present moment, I feel that a polite scepticism is the attitude to be taken.

DR. FINNEY: From the surgical standpoint, I should like to add one word. I have been unfortunate enough, as have most surgeons, to lose two or three cases following operation upon the thyroid. In one or two of these cases, the operation was a simple ligation and was followed by death in from 48-60 hours. All the cases, with one exception, that I have seen die from operations upon the thyroid, have died in practically the same way, not immediately, but after two or three days. It seemed to me that some process, just what I do not know, had been started at the time of operation which simply kept on in spite of everything that was done, until the patient died with symptoms very strongly suggesting an intense intoxication of some sort. It appeared then, reasoning purely empirically, that if these patients died from the least thing surgically that one could do, they could not do more than die if the most that one could do was done. I was tempted to put this idea into practice in apparently one of the most hopeless cases that I had operated upon up to that time. I felt that if I did simply so much as a ligation of a vessel and stopped there, the patient would surely die in the manner just described. I had tried, as Dr. Barker suggests, to build the patient up under the rest treatment but there had been no permanent benefit, as unfortunately is sometimes the case. We then resorted to surgery. I removed almost the entire thyroid with the exception of a small piece no larger than the tip of my finger. The patient did just what one would reasonably expect. She was extremely ill for the first 24-48 hours, when a most remarkable change took place and the pulse rapidly came down to normal and remained there. The patient was operated upon two years ago. I heard from her only a short time ago and she had had no recurrence of her symptoms. Since then I have operated upon a group of about 20 cases, among them some of the most unfavorable cases I have had to deal with. I have no definite explanation to offer other than that it is reasonable to suppose, and indeed generally accepted, that in some way or other the thyroid is concerned with the group of symptoms presented by these patients. Probably the internal secretion of the thyroid and parathyroid is coupled with that of the thymus and the adrenals and perhaps others of the ductless glands and a vicious circle of some sort formed. It would seem that if that vicious circle could be broken beyond repair, the situation could be controlled. If so much thyroid is taken out that there can be no comeback, I thought that perhaps this could be accomplished. That was the idea of the operation. So far, I have had no fatal results. All the patients have followed practically the same course. The charts of these cases are most striking looking. Immediately after the operation, the pulse rises to 160-180. Indeed, sometimes it cannot be counted with certainty. The first 24 hours are an anxious time. If the patient lives through this period, I am confident she will do just what the others have done, *i. e.*, make a good recovery. Here again I feel according to my experience that the old treatment of these thyroid cases is not correct. Most authors advise against the use of morphia and digitalis. It seems to me, however, that these two drugs are especially indicated. I have been in the habit of giving them morphia enough to keep them quiet, and also enough digitalis to steady the heart's action. We have gone on that principle and, so far, the patients thus treated have all done well. Of course, I am constantly expecting to have one who will not do well. It is perhaps expecting too much to think that they will all do well.

In regard to this method of treatment of Graves' disease, I am not making any extravagant claims, I am simply stating my experience up to date. The list of cases operated upon in this way, and the results, seem to me sufficiently long now to justify the further use of the method and also would seem to uphold, perhaps a little more strongly than heretofore, the position occupied by most surgeons.

DR. HALSTED: I should be sorry to emphasize the issue which seems to have arisen between the surgeons and physicians. Dr. Finney and I evidently are in agreement that the medical men should be given a chance, but not too much of a chance, in the treatment of cases of Graves' disease.

It is quite true, as Dr. Janeway says, that many patients are not cured by operation. In our experience this has very largely been due to the fact that not enough thyroid has been removed. The usual operation, the world over, is lobectomy on one side only. When a lobectomy on both sides has been done the patient has with very few exceptions been satisfactorily cured. As to the absolute cures, the percentage in our experience is much smaller than is universally claimed. Usually some traces of the disease remain. We have carefully restudied our cases during the past three years, and conclude that in not more than 25 per cent of the one-sided lobectomies were there no symptoms, discoverable by an expert, remaining. But certainly in 50 or 60 per cent the patients are satisfied with the results.

I should be interested to know if Dr. Finney has observed symptoms of hypoparathyroidism in any of his cases of complete excision of the thyroid gland.

DR. FINNEY: None at all.

DR. HALSTEAD: Dr. Janeway recalls six or more cases which have been permanently cured by medical treatment. The surgeon can quote larger figures. There are many surgeons who credit themselves with more than a hundred cures, and two or perhaps three with a thousand.

With reference to feeding of the thymus, Mikulicz, I think, was the first to suggest it. Many years ago we practiced it in some cases but without significant result. The improvement which has occasionally been reported from feeding of the thymus gland may be analogous to that observed from thyroid feeding in the early thyroid hyperplasias, in the so-called parenchymatous goiter. In cases of this kind the glandular swelling may be reduced while the patient's symptoms are aggravated from the administration of the thyroid extract.

DR. BARKER: There ought to be no conflict between the physicians and the surgeons in the treatment of exophthalmic goiter, and, of course, there is not in this hospital. What we need is the best kind of team-work between physicians and surgeons. A physician will do well to try the effect of judiciously selected medical measures first, but it is wrong to keep an outspoken case of Graves' disease long from the surgeon if the patient does not respond favorably to treatment. It is not right to let the patient go on for a long period with severe thyroid intoxication, until the heart muscle becomes greatly injured, and the surgeon has no chance. This discussion has, I think, emphasized the necessity of a combination of the best work of physicians with the best work of surgeons adequately to care for these patients.

DR. THAYER: I should like to add one word to what Dr. Barker has said. One's position with regard to these cases is not unlike the position of the practitioner with relation to certain instances of appendicitis, particularly some years ago. I think most medical men who practice in a community where they have surgical friends in whom they have confidence, feel it their duty in case of doubt to have a surgeon see the case of appendicitis immediately. I feel in the same way with regard to these instances of thyroid disease. I rarely see a well-marked instance of hyperthyroidism without talking it over with a surgeon at the outset. Such cases should early be observed by both physician and surgeon. I never tire of telling of a case I followed here many years ago—a nurse. I saw her early one morning and advised waiting a little while. Soon I felt that operation was urgent. By 9 o'clock Dr. X. saw her and advised waiting. When he was ready to operate, Dr. Y. saw her and advised a further stay. When he was about to operate, Dr. Z. in turn advised that we wait a little longer. When, finally, the operation was performed, it was almost too late. It has always seemed to me very silly on the part of the physician to constitute himself the supreme judge to decide when a case of hyperthyroidism should be turned over to the surgeon. I know of few conditions where it is more important that the physician and surgeon should proceed hand in hand, as Dr. Barker has said, from the outset. The conscientious practitioner, whether physician or surgeon, is apt to lean toward conservatism. The wise surgeon is not inclined to act immediately in a situation where there has been room for doubt as to the proper method of procedure; and the physician should not expect the surgeon to accept his conclusion without proper deliberation. It is sometimes much to the advantage of the patient if that deliberation is shared by both surgeon and physician from the outset.

DECEMBER 21, 1914.

Paroxysmal Hæmoglobinuria. Exhibition of Case. DR. G. A. BATTEN.

Male patient aged three and a half years. Father and mother and two older children living and well. No history of lues in family. Nothing in past history bearing on present illness, there being especially no history of early luetic manifestations. The present illness began with sudden onset on November 1 of this year. Patient had a chill, fever and afterwards was said to have voided bloody urine for a period of about one week. After this he was apparently well, except that he was slightly pale, until December 12, when he had another chill and again voided bloody urine. He was brought to the hospital on December 15, three days after the onset of the last attack.

On examination: very pale, enlarged liver and spleen; general glandular enlargement, also slight jaundice. The blood showed w. b. c. 29,000, r. b. c. 1,800,000, hæmoglobin 37 per cent. On examination the urine was found to be black in color, and gave a distinct guaiac test. Microscopic examination showed a few white blood cells, a few granular casts, but no red blood cells. The patient was put to bed. A specimen of urine examined 24 hours later was practically normal, was light amber in color and there was no hæmoglobin present. Because of the history and because he had a hæmoglobinuria which cleared up 24 hours after being put to bed, we thought we had to deal with a case of paroxysmal hæmoglobinuria. As further evidence that this was a case of true paroxysmal hæmoglobinuria, we did a test first described by Donah and Landsteiner and subsequently confirmed by Dr. Moss, working in this hospital, and many others. These observers found that hæmolysis of the blood of hæmoglobinuric patients took place if the temperature was first lowered and then raised. To do this test we placed 0.25 cc. of the patient's serum in each of two test tubes and to each we added 0.25 cc. of a 5 per cent suspension of the patient's corpuscles. We reduced the temperature of one to 0° and then raised it to 37°, when complete hæmolysis promptly took place. The other tube was kept at 37° without first lowering to 0°, and no hæmolysis resulted.

In this case it seemed reasonable to us to explain the general glandular enlargement and the enlarged liver and spleen on the basis of hereditary syphilis, and the anæmia as a result of this infection, plus the severe hæmoglobinuria. The relationship of syphilis and paroxysmal hæmoglobinuria seems to be a close one. An analysis was made by Cook in the *American Journal of the Medical Sciences*, 1912, of all the cases reported prior to that time. He found that 90 per cent of the cases gave a positive Wassermann. Whether or not a positive Wassermann in this disease is due to a luetic infection, or whether it may be due to some other condition, I do not wish to discuss now. In this case it seems justifiable to make a diagnosis of hereditary syphilis because of the clinical findings, and also because of the fact that both the blood of the patient and that of his mother gave a positive Wassermann.

DISCUSSION.

DR. THAYER: I should like to know if there was any hæmoglobinuria while in the hospital?

DR. BATTEN: None after the first day of hospital care.

DR. THAYER: We had several years ago a very remarkable instance of hæmoglobinuria in a woman with a very striking anæmia which bore some resemblance to pernicious anæmia. The hæmoglobinuria showed a remarkable periodicity, appearing regularly over considerable periods of time in the early morning hours, say from 4-6 o'clock. We tried in many ways to see if we could not produce this same condition at some other hour, but unsuccessfully. The patient came to the hospital for this condition on two successive years, each time having a moderately enlarged spleen. The Wassermann reaction was negative. In view of the interesting results following splenectomy, the possibility of performing the operation for her anæmia entered our minds. Was there any periodicity in the case exhibited to-night?

DR. BATTEN: No, there was none whatever.

*** Gaucher's Disease, with Report of Two Cases in Infancy.** DR. J. H. M. KNOX, JR., and DR. W. H. WAHL, Cleveland, Ohio.

The cases which form the basis of this report are those of two infants, one of whom is at present in the Harriet Lane Home of this hospital.

The first patient, a girl 9 months old, was brought to the Thomas Wilson Sanitarium in June, 1912, with a history of never having gained. There was no history of acute onset, nor of very marked digestive disturbances. She had begun cutting her teeth at about 7 months; had never walked and could not hold her head up. The family history was of importance. The patient was Jewish, the youngest of 11 children, 3 of whom had died in infancy.

* This report will appear in full in a subsequent issue of THE JOHNS HOPKINS HOSPITAL BULLETIN.

and one at the age of 14 with what was said to be tuberculosis of the hip. Six children were living and well. The history at the sanitarium was uneventful. There were almost no symptoms of acute intestinal derangement; there was some indigestion and now and then distension, which was relieved for a time, only to reappear later. The patient lost progressively in weight and died, at the age of 11 months, of exhaustion. Repeated von Pirquet tests were negative. The Wassermann was negative. Physical examination on admission showed a pale child, with slight bronzing of the skin, more pronounced over the face. No jaundice. Enlargement of abdomen due to tremendous hypertrophy of both liver and spleen, the latter extending considerably below the umbilicus, firm and hard to the touch but rather smooth. The liver extended to about the same level, the left lobe extending 1 or 2 inches below the costal margin. On palpation it was firm and gave an impression of tenseness and a certain degree of resiliency. There was only a slight general glandular enlargement. The blood-picture was almost normal. The leucocytes ranged from 10,000-22,000 on several counts. Two or three days before death they rose to 35,000. The differential count showed about an equal proportion of mononuclear and polynuclear cells, until shortly before death when, with the increase in the leucocytes, there was a marked increase in the mononuclear element. No diagnosis was made. We discussed Banti's disease, although this is of extremely rare occurrence at this age. The last blood count led us to think that we had perhaps missed a case of lymphatic leukemia. The autopsy was done by Dr. Wahl.

Some 16 months later, the same mother brought to the dispensary at the Harriet Lane Home, a second child, almost the counterpart of the one seen at the Thomas Wilson Sanitarium, an infant of 4 months, with no history of acute onset, breast fed exclusively, but one who had never thrived. The patient presented an enormously enlarged liver and spleen, together with slight general glandular enlargement. It weighed only 8 lbs. She was treated in the dispensary for several months and was afterwards admitted to the house, where she still remains. She has had slight leucocytosis, ranging from 11,000 to 26,000. At Dr. Howland's suggestion, treatment with radium was begun in October. The leucocytes fell in a few days from 20,000 to about 6400 and have remained extremely low since, the last count being about 2200.

The findings at autopsy on the first case and the examination microscopically of a gland removed from the second child, showed the same characteristic cellular changes which were first described by Gaucher in 1882. Since then 18 cases have been definitely proven at autopsy or by examination of the spleen following operation to belong to this group. It is interesting that only two of these patients have been males. The age seems to be unimportant, because of the long duration of the disease. If our two patients belong to this group, they are apparently the youngest whose cases have been reported. The oldest patient, above 18, was 44 years old.

Dr. Knox then referred to the most characteristic symptoms and physical signs of the condition, which apparently does not descend from one generation to another, but frequently appears in several children of the same generation. As to results, one can only say that the disease is a long and tedious one. Splenectomy was done in 9 cases and there were 3 deaths immediately following the operation. In the 6 other reported cases, the patients were living. The chief relief from operation has been in the removal of the large abdominal mass. The disease itself has not been checked.

Dr. Knox was followed by Dr. Wahl, who first described the anatomical findings of the organs and glands, taken from Case I, macroscopically and then exhibited various microscopical sections of the same. In all the organs the same condition was marked, clusters of large, pale cells, somewhat resembling fat cells, being predominant. As to the exact nature of these cells, Dr. Wahl declined as yet to give any definite opinion, but he called particular attention to the marked infiltration by them of each organ and to the apparent activity of their growth.

DISCUSSION.

DR. HOWLAND: To the conditions which have generally been recognized as causing enlargement of the spleen in infancy must be added another. This, up to the present time, has not been appreciated. It is one that would hardly be thought of, for manifestations of Gaucher's disease in infants, if these cases are to be considered Gaucher's disease, are quite different from those in older children or adults. The course of the disease is much more rapid, the lesions more widely spread and the splenic enlargement relatively not so great. Years ago, as a hospital interne, I saw the patients reported by Bovaird. They were older children, the disease had been recognized for several years and in each case the spleen filled two-thirds of the abdomen. The microscopic changes in the spleen and other organs have been described as specific, and if this is so it would seem that these two cases described by Dr. Knox should be classed under Gaucher's disease, even though clinically they are so different from the reported cases.

DR. JANEWAY: I have been much interested in this presentation as I had the opportunity of seeing a few of the previously reported cases, among others the family group presented by Brill, Mandelbaum and Libman. It may interest the society to know just how these cases came to be so beautifully studied. There were four members of the family with enlarged spleens. The first case came to autopsy as the result of a pericarditis and the diagnosis was made in this way. The second case happened to meet with a bicycle accident within one block of Mt. Sinai Hospital in New York and was brought in and came to autopsy. But for that, it would probably never have been added to the list.

I saw the case of Downes before operation. It brought up certain problems of diagnosis and added very considerably in my mind to the difficulty in distinguishing these splenomegalies. The patient was a young woman from the South, with no family history of enlarged spleens. She had had rather marked anæmic attacks, dating back to early life. Some of these had been of considerable severity, so that she was incapacitated. She was a musician and for months at a time would have to give up practicing on account of her extreme weakness. When I saw her, she had been observed in the New York hospital for some weeks. She was suffering from severe secondary anæmia, with extreme leukopenia the white cells always being below 2000 and frequently below 1000. She had a large spleen, liver just palpable and nothing else. The picture, with the excessive leukopenia, was so suggestive of splenic anæmia, or the early stage of Banti's disease, that I gave that as my opinion. The operation was a successful splenectomy. The sections were carefully examined and there was no question as to the diagnosis of endothelial hyperplasia.

It seems to me, therefore, that the clinical picture of Gaucher's disease is to be considered as one which scarcely permits of positive diagnosis. With a familial history, the diagnosis may be made with certainty, but in the absence of such history it may be impossible to separate it from the so-called splenic anæmia.

DR. THAYER: I asked Dr. Knox a few moments ago if he were familiar with the case of Stengel, which was reported some years ago before the Association of American Physicians. He tells me that Brill has ruled it out. Stengel's microscopic specimens bore a striking resemblance to those shown here to-night. His case was one regarded as Banti's disease until operation. On examination of the spleen after splenectomy, the striking feature was that the endothelial masses stood out so plainly, just like definite tumors. Indeed they could be seen on the surface of the spleen. It was remarkable that it had not been felt as a nodular spleen *intra vitam*. The structure of these areas was very similar to that shown in the sections by Dr. Wahl to-night. Of course I speak from memory, but should be glad to know why Brill ruled that case out. I remember that there was a great deal of discussion at the time, and I believe Dr. Welch acquiesced in the view that the case was an instance of Gaucher's disease.

DR. WAHL: I think I can answer your question. Dr. Karsner of Cleveland was the man who did the autopsy on Stengel's case. Later on they found tuberculosis. Dr. Karsner thought the case might have been one of Gaucher's disease, but on account of the presence of the tubercle bacillus and of definite tubercles the other men were doubtful and so the case was ruled out.

Medical Experience in Siam. DR. E. C. CORT.

After a brief outline of the topography of the country and the ethnology and religion of the people, Dr. Cort discussed the principal diseases found in Siam. The sanitary conditions of the country are practically nil and the people know nothing of the cause of disease or of its prevention.

Small-pox is extremely common and no precautions are taken by the natives against the disease. Vaccination has been introduced, however, where Western civilization has penetrated.

Malaria prevails generally, 90 per cent of the people examined by Dr. Cort showing signs of chronic malaria. Although the disease is practically endemic, severe epidemics are not infrequent with large numbers of cases of the cerebral type, the attacks coming on as quickly as apoplexy. In these instances, a patient who had perhaps been having fever, would suddenly fall absolutely unconscious and remain in coma until death. The parasite was usually the æstivo-autumnal, of a very malignant form.

Infection with the hookworm is very common, some statistics indicating that at least 90 per cent of the people harbor the parasite.

Tuberculosis also is extremely common. The natives, of course, have no ideas with regard to the care and treatment of the patients. The only thing that saves a great many is the fact that the native architecture is of such a type as to prevent them from closing their houses tightly, and in this way they get a certain amount of fresh air and sunlight.

Another disease frequently encountered is dysentery, very largely of the amœbic type. The use of emetin in the treatment of this disease has been most interesting. One male patient with acute dysentery was having 60 stools a day, practically pure mucus and blood. He was extremely anæmic and very weak. He was put on emetin, one-half grain every four hours, with a little morphia and strychnine. Although he came into the hospital on a stretcher, he went home at the end of five days, carrying his own baggage, saying he felt too well to stay any longer. At the end of seven or eight weeks, his daughter reported that he was still in very good health. The result was very remarkable, as he must have had severe ulceration. Dr. Cort mentioned other striking results obtained from the use of emetin, among them a case of amœbic abscess and one of enlarged liver.

An interesting condition to be investigated is that of beri-beri, which is popularly supposed to be due to eating over-milled rice. A severe epidemic of both the wet and dry forms (fatal to 50 per cent of the patients involved), which followed a flood some years ago, would seem to indicate that perhaps other factors than the eating of over-milled rice are involved in the causation of this disease.

Leishmania infections form another group of cases to be cleared up. Dr. Cort had had five such cases, all the patients coming from the same mountain district. In one the spleen actually extended into the pelvis.

Venereal disease, which is almost unknown in the country districts, is quite common in the cities, particularly the seacoast towns. Over 90 per cent of the officers and men in the army, and also government employees, are infected with one or both diseases. The marriage and divorce customs are extremely lax, and this factor greatly aids the spread of the infection.

The most common surgical infection is calculus, the patients ranging from six months in age to 83 years. With one or two exceptions, every case of calculus in men over 30 seen by Dr. Cort, was accompanied by arteriosclerosis. The latter condition is extremely prevalent in men of 40 and older.

Leprosy is of frequent occurrence, the afflicted persons congregating in leper villages after having been driven from their homes.

Eye cases are also very numerous.

With less than ten doctors for many millions of people, Dr. Cort spoke of the hope of establishing a medical school in Siam, which would provide for the training of competent natives to help cover this enormous field.

THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB.

DECEMBER 14, 1914.

Superstition and the Doctor. MR. OWEN WISTER.

TITLES OF PAPERS APPEARING DURING THE YEAR, ELSEWHERE THAN IN THE BULLETIN, BY PRESENT AND FORMER MEMBERS OF THE HOSPITAL OR MEDICAL SCHOOL STAFF.

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NOTES ON NEW BOOKS.

Sclero-Corneal Trephining in the Operative Treatment of Glaucoma. By ROBERT HENRY ELLIOTT, M. D. Second edition. $3 net. (*New York: Paul B. Hoeber, 1914.*)

It is interesting to note that this work has passed into its second edition before the end of its first year of life. That the question of sclero-corneal trephining for glaucoma has appealed to the common sense of ophthalmologists all over the world is evident from the widespread interest Col. Elliott's work has aroused, and few will be found without the first edition. The book has been so generally reviewed and its points subjected to such sifting in medical discussions within the past year that little remains to be said of this new edition. The chapter dealing with sclero-corneal trephining (Chapter V) has been greatly expanded. Chapter XI has been completely revised and here one will find the results of four years of trephining in Madras. Chapter XII is new and puts forward the experience and statistics of a number of ophthalmologists.

Those who have tried this operation are pretty well agreed that it is especially valuable in chronic simple glaucoma. It seems equally clear that is has not converted nor probably ever will convert many to the view of its superiority over iridectomy in acute inflammatory glaucoma. In chronic non-inflammatory glaucoma it is perhaps a better procedure than iridectomy, but even here, by treading on better known ground and doing the iridectomy, one might after all, certainly in many cases, be subserving the best interests of the patient. One should bear in mind that iridectomy, even in chronic simple glaucoma, has saved its thousands and while there remains much to be desired on this point we are hardly called upon as yet to abandon the procedure entirely. It seems that the performance of an iridectomy along with the trephining has a very important influence for good upon the outcome of this operation and that we cannot afford to omit this step. When we come to the question of the remote or ultimate results of the operation we confess to a feeling of some little pessimism and we are convinced that the last word upon this question cannot be spoken for several years. It is hard to believe that an eye with an opening into its interior covered by a prominent bleb, with constant friction going on between the surface of the bleb and the upper lid and with bacteria everywhere on the surface of the conjunctiva, can escape infection for very long. We are still in the dark as to the true nature of glaucoma and from recent reports it would seem that late infection might after all prove the ultimate undoing of many of these cases.

A Manual of Practical Hygiene. By CHARLES HARRINGTON, M. D., Fifth edition. Revised and enlarged by MARK WYMAN RICHARDSON, M. D. (*Philadelphia: Lea & Febiger, 1914.*)

This well-known work was first revised several years ago by Dr. Richardson, who edited the third edition shortly after Dr. Harrington's death. Since then a fourth and now a fifth edition has appeared. This last edition has had the benefit also of the collaboration of the officials of the State Board of Health of Massachusetts of which Dr. Richardson is secretary. The original form of the book is preserved, and the treatment of the various branches of the science remains as exhaustive as it was formerly. On the chemical aspects of hygiene the book is especially strong, and the chapter on foods, comprising 289 pages and divided into eight sections, is one of the most comprehensive presentations of this subject in English. The chapter dealing with hygiene of occupations, prepared by Dr. William A. Hanson, is especially attractive and is illustrated by a number of instructive photographs. Military hygiene is also ably presented in a section of 60 pages, and naval and marine hygiene somewhat more briefly. Medical inspection of schools is considered by Mr. George H. Martin, formerly secretary of the State Board of Education, and is an excellent résumé of the duties of medical school inspectors.

Considering the great importance of school hygiene, however, the treatment of this subject seems inadequate. We look in vain for some detailed discussion of the important questions which arise in regard to school children. How many hours of work, for instance, should be required of children of various ages? What should be the hours of school attendance and how should they be distributed? At what age should children begin school? Should attendance at kindergartens be encouraged? These and many other questions are vital and need an answer from the medical and from the educational point of view. A still more important question possibly relates to the intimate relationship between the incidence of infectious diseases in a community, and the age at which school attendance is compulsory, a topic emphasized so much by the English sanitarians. A book which is so distinctly the standard reference book on hygiene in America should, we feel, give more complete and thorough discussion of such questions, although this criticism is equally applicable to the other text-books on hygiene published in this country. All in all, Richardson's edition of Harrington, we predict, will remain for a long time our best authority in this field. W. W. F.

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